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16 UNITED STATES DISTRICT COURT  
17 SOUTHERN DISTRICT OF CALIFORNIA

18 GEN-PROBE INCORPORATED,

19 Plaintiff,

20 v.

21 VYSIS, INC.,

22 Defendant.

No. 99CV2668 H (AJB)  
THE HONORABLE MARILYN L. HUFF

**PLAINTIFF GEN-PROBE INCORPORATED'S  
MEMORANDUM OF CONTENTIONS OF FACT  
AND LAW**

**[Local Rule 16.1 (f)(3)]**

Pre-Trial Conference: February 4, 2002  
Time: 10:30 a.m.  
Place: Courtroom 1

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1 **I. INTRODUCTION**

2 Plaintiff Gen-Probe Incorporated ("Gen-Probe") submits this Memorandum of Contentions  
3 of Fact and Law pursuant to Local Rule 16.1(f)(3) and the Court's December 6, 2001 Order  
4 Granting Vysis, Inc.'s Ex Parte Motion for Continuance of the Final Pre-Trial Conference and  
5 Associated Deadlines.

6 **II. CONTENTIONS OF FACT**

7 **A. THE PARTIES**

8 1. Gen-Probe was founded in San Diego, California in 1984 as a small "start up"  
9 company, seeking to develop products based on the discoveries of a local research scientist. Gen-  
10 Probe has grown over time to become one of the largest biotechnology companies in San Diego.  
11 Gen-Probe maintains its principal offices and research facilities at 10210 Genetic Center Drive,  
12 San Diego, California 92121, where it employs over 500 scientists and staff. Gen-Probe is  
13 organized under the laws of the State of Delaware.

14 2. Defendant Vysis, Inc. ("Vysis") was formed in 1991. Vysis is the successor to  
15 Gene-Trak Systems, Inc. As used herein, "Vysis" refers to Vysis and to its predecessors-in-  
16 interest, including Gene-Trak Systems. Vysis is engaged in the business of developing products  
17 used in the evaluation of genetic diseases and maintains its principal place of business in Downers  
18 Grove, Illinois. Vysis is organized under the laws of the State of Delaware. Until December 2001,  
19 Vysis was controlled by BP Amoco, Inc. Vysis is now a wholly-owned subsidiary of Abbott  
20 Laboratories, Inc.

21 **B. BACKGROUND REGARDING THE TECHNOLOGY AT ISSUE**

22 3. Living cells store genetic information in molecules of nucleic acid known as DNA.  
23 These molecules consist of long, thin strands that, in turn, are usually found in the form of two  
24 tightly bound, complementary chains. DNA molecules contain their genetic information in the  
25 form of a genetic code. The information in the DNA determines the life processes of each  
26 organism. DNA is used to make related nucleic acid molecules called RNA, which are used to  
27 transfer the information to cell components that manufacture proteins that are used to determine  
28 the structure and function of the cell.

4. Through the work of its scientists and staff, Gen-Probe has developed and continues to develop diagnostic tests that seek out the DNA or RNA of infectious organisms. These types of tests are generally referred to as "genetic probe tests" or "nucleic acid tests" ("NAT"). Gen-Probe now markets DNA probe products that test for a wide range of microorganisms that cause tuberculosis, strep throat, pneumonia, fungal infections and sexually transmitted diseases. Through the efforts of its scientists and staff, Gen-Probe has emerged as a recognized world leader in the development, manufacture and commercialization of diagnostic products based on its patented genetic probe technology. Gen-Probe has received over 40 FDA clearances and approvals for genetic probe tests to detect a wide range of microorganisms, including *Chlamydia trachomatis*, *Mycobacterium tuberculosis*, and *Neisseria gonorrhoeae*.

5. Many human diseases are caused by bacterial or viral agents that invade living cells. Most often, the presence of these bacterial or viral agents was detected directly by growing them in culture or indirectly through the detection of antibodies. Unfortunately, it takes time, sometimes weeks or months, to isolate organisms in culture, and it usually takes months for the body to manufacture antibodies in sufficient amounts to reveal the presence of infectious agents. Consequently, these methods do not lend themselves to early detection of infection. NAT addresses this problem.

6. Among the disease detection technologies recently applied by Gen-Probe in its NAT products is its patented nucleic acid technology known as "Transcription-Mediated Amplification" ("TMA"). This technology enables Gen-Probe's NAT products to detect extraordinarily small quantities of the nucleic acids of infectious agents.

7. In September 1996, Gen-Probe received a \$7.7 million grant from the National Institutes of Health to develop TMA-based nucleic acid tests to be used in screening donated blood for human immunodeficiency virus (HIV), the causative agent of AIDS, and hepatitis C virus (HCV), which causes a severe form of hepatitis.

8. At the time of the NIH grant to Gen-Probe, donated blood was principally tested by procedures that detected the presence of antibodies to the viruses being screened. Due to the time it takes for the body to make antibodies after initial infection, donated blood may test negative for

antibodies, yet still carry infectious viruses. This delay between the time of actual infection and the time that antibodies can first be detected is often known as the "window period." Reduction of this "window period" was a significant concern of the United States government and the primary focus of the grant to Gen-Probe to develop NAT diagnostics for use in blood screening.

9. In fulfilling its obligations under the grant, Gen-Probe developed NAT tests to detect the nucleic acids of HIV and hepatitis C virus in blood. Through the use of its NAT test, Gen-Probe believes that researchers and medical personnel will be able to rapidly and *directly* detect the presence of genetic material of viruses like HIV and HCV more accurately. As such, Gen-Probe believes that its new test may significantly reduce the "window period" for detection of these extremely harmful viral agents and resulting diseases.

10. Final development of the NAT tests for blood screening in the United States is now taking place in testing conducted by the American Red Cross, America's Blood Centers, and others. Use of the tests in the United States is made pursuant to an Investigational New Drug Application filed with the United States Food and Drug Administration. In blood tested by the American Red Cross, Gen-Probe's products have detected hepatitis C virus and HIV which escaped detection by prior methods.

11. Gen-Probe has entered into an agreement with Chiron Corporation ("Chiron") of Emeryville, California, with respect to the development, manufacture, and distribution of blood screening products. Gen-Probe is also a party to an agreement with Bayer Corporation ("Bayer") of Emeryville, California with respect to the development, manufacture, and distribution of clinical diagnostic products for the detection of HIV and hepatitis C virus, among other pathogens.

12. All of the Gen-Probe products are manufactured in San Diego, California.

#### C. THE '338 PATENT

13. The United States Patent and Trademark Office issued United States Patent No. 5,750,338 (the "'338 Patent") on or about May 12, 1998. The '338 patent was based upon United States Patent Application No. 08/238,080, which was filed on May 3, 1994.

14. Vysis claims to be the owner, by assignment, of the entire right, title and interest of the '338 patent. Vysis contends the '338 patent has a priority date of December 21, 1987.

1           15. The '338 patent relates generally to methods for use in nucleic acid diagnostics,  
2 including the use of nucleic acid "probes" to detect infectious organisms. In particular, the '338  
3 patent relates to methods by which scientists may "capture" nucleic acid molecules onto solid  
4 supports and copy (or "amplify") those molecules so that small quantities of these molecules then  
5 may be detected by probes. The scientific concepts relevant to this require an understanding of  
6 nucleic acids and nucleic acid probes as well as techniques for target capture and amplification.

7           16. In relation to the '338 patent, as of December 21, 1987 one of ordinary skill in the  
8 art would be considered to have been an individual with a postgraduate degree in the biological  
9 sciences and 5 to 7 years relevant post-graduate research experience in molecular biology. Such  
10 experience would have allowed the individual to develop the skills of a molecular biologist using  
11 the techniques of DNA and RNA isolation and characterization, cDNA synthesis, cloning, liquid  
12 and solid phase hybridization, isotopic and non-isotopic labeling methods, DNA sequencing  
13 methods, and nucleic acid amplification.

#### 14           1. Nucleic Acids

15           17. Nucleic acids are molecules that store and transfer genetic information in all living  
16 organisms. The two main types of nucleic acids are DNA (deoxyribonucleic acid) and RNA  
17 (ribonucleic acid). DNA functions as a stable repository of genetic information, while RNA  
18 typically serves to transfer the information stored within DNA to the cell's machinery for making  
19 proteins.

20           18. DNA and RNA are both composed of chains of chemical sub-units called  
21 "nucleotides." Each nucleotide has three components: a sugar, a phosphate group, and a "base"  
22 containing nitrogen. There are four types of nucleotides in DNA, each of which has a different  
23 base: adenine, thymine, guanine, or cytosine (abbreviated A, T, G, and C). The nucleotides in  
24 RNA are A, G, C and uracil (U).

25           19. The "sequence" of the individual A, T, G, and C nucleotides in a DNA molecule  
26 encodes the genetic information that instructs the cell how to make particular proteins. Because  
27 DNA sequences determine which proteins a cell will make, it is differences in their DNA  
28 sequences that make the cells of one organism differ from the cells of another.

20. DNA in cells ordinarily occurs in a molecular structure in which two "strands" of DNA are specifically bound to one another in a structure that resembles a twisted ladder. In double-stranded DNA, the nucleotides on opposing strands of the ladder are always paired in a precise way. An "A" nucleotide binds only to a "T" nucleotide on the opposite strand, and vice versa. Likewise, a "G" nucleotide binds only to a "C" nucleotide, and vice versa. Each combination of an "A" nucleotide with a "T" nucleotide (or a "C" with a "G") is referred to as a "base pair." The way in which each type of nucleotide binds only to one other type of nucleotide is called "complementary base pairing." As a result of complementary base pairing, the sequence of nucleotides on one strand of a DNA molecule necessarily determines the sequence of nucleotides on the opposite strand. Complementary base pairing is substantially the same for RNA, using "C" paired with "G" and "A" paired with "U."

## 2. Nucleic Acid Probes

21. By exploiting the natural feature of complementary base pairing, scientists can use pieces of nucleic acid as "probes" to detect the presence of a target nucleic acid in a test sample. If two complementary pieces of nucleic acid are present in a solution under the right conditions, the complementary bases will bind together or "hybridize" to form double strands. This phenomenon is commonly known as "nucleic acid hybridization." Nucleic acid hybridization techniques can be applied in a diagnostic test to detect an infectious organism (the "target" organism) by the use of a probe that is designed to be bind specifically to a nucleic acid sequence that is known to be unique to the target organism.

22. In theory, if the target organism is present in the sample, the "probe" should bind to the target organism's nucleic acids because the sequence of the probe has been designed to be complementary to it. By attaching a detectable "label" to a probe, scientists are then able to determine how much, if any, probe has bound to sequences from the target organism.

## 3. Target Capture

23. Target capture techniques are used in nucleic acid methods to isolate a particular nucleic acid of interest prior to detection or other steps. In target capture methods, the target nucleic acid is bound to a solid support, such as a filter, particle, or a bead, which allows the target



1 to be separated from the rest of the sample. The immobilized target nucleic acid is detected with a  
2 probe, amplified prior to detection, or used for other purposes.

3       **24.** The target nucleic acid can be immobilized on the solid support either by direct  
4 attachment or by the use of a "capture probe" or other intermediary that forms a bridge between  
5 the support and the target nucleic acid. A capture probe is a nucleic acid sequence that is designed  
6 to bind with the target organism's DNA or RNA and also attach to the solid support.

#### 7               **4. Amplification**

8       **25.** Often, it is necessary to detect very small numbers of infectious organisms in a  
9 sample. This is particularly true when screening for the presence of the organism in the absence of  
10 a full-blown infection. Examples include screening blood intended for transfusion for the presence  
11 of viruses such as HIV. In these situations, the presence of even small numbers of organisms may  
12 lead to the transmission of infection from one individual to another.

13       **26.** The classic way to detect low numbers of organisms is to transfer the sample to  
14 culture media that will support the growth of the organism. After a suitable time, the number of  
15 organisms will generally have increased sufficiently to allow them to be detected directly by  
16 hybridization or other methods. Growing organisms in culture is slow, costly, and inconvenient,  
17 and some important pathogenic organisms cannot be cultured in the laboratory. A better approach  
18 is to rapidly increase the target organism's nucleic acid in the laboratory through processes known  
19 as "nucleic acid amplification." Amplification procedures are generally performed with enzymes  
20 and primers. Enzymes are protein molecules that catalyze biological reactions. "Polymerase"  
21 enzymes are used to copy a DNA or RNA strand to make its complement and occur naturally in  
22 cells. These enzymes are normally used in cellular processes to make copies of genes to be passed  
23 on to its progeny. Polymerase enzymes may be either specific or non-specific in the manner in  
24 which they copy nucleic acids.

25       **27.** Scientists have learned to use enzymes such as polymerase to increase the amount  
26 of a DNA or RNA in sample up to a billion-fold in a matter of minutes. By making multiple  
27 copies of the target organism's nucleic acids, the amount of target that is available to bind with a  
28 probe in a detection step is increased to easily detected levels, thus increasing the "sensitivity" of

1 the assay.

2       **28.** Primers are used in amplification processes to provide starting points for the  
3 synthesis of nucleic acids by enzymes such as polymerase. The primers used in amplification  
4 processes can be either specific or non-specific. "Specific" primers are carefully designed to bind  
5 only to a pre-selected nucleic acid sequence of a particular target organism, usually a sequence  
6 selected to be unique to that organism. Non-specific or "random" primers can be used with DNA  
7 polymerases to copy random portions of any nucleic acid sequence in the target organism. When  
8 random primers are used, the resulting amplification process is referred to as "non-specific"  
9 because DNA synthesis begins at random locations all over the target nucleic acid. Other non-  
10 target nucleic acids that may be present in the sample are also amplified. Using random, non-  
11 specific primers avoids the work required to select, make, and test specific primers for each  
12 individual target organism.

13       **29.** The Court has previously construed the claims of the '338 patent to encompass  
14 only non-specific amplification.

15       **D. GEN-PROBE'S PRODUCTS DO NOT INFRINGE THE '338 PATENT**

16       **30.** Gen-Probe's NAT test kits for use in detecting HCV and HIV in the nation's blood  
17 supply, which utilize Gen-Probe's own patented Transcription Mediated Amplification ("TMA")  
18 method, do not and will not infringe any valid claims of the '338 patent.<sup>1</sup>

19       **31.** Vysis has asserted that Gen-Probe's products infringe claims 1, 2, 3, 4, 5, 7, 8, 9,  
20 10, 11, 13, 14, 24 and 25. Claims 1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 13 and 14 are method claims that are  
21 directly infringed only in the practice of the method. Claims 24 and 25 are apparatus claims to a  
22 kit. However, as set forth below, those claims are written in means-plus-function format under 35

23  
24 <sup>1</sup> At the time it filed its complaint, the only commercial products that Gen-Probe was distributing  
25 that incorporated any type of target capture and nucleic amplification consisted of its NAT test kits  
26 for detecting HIV and HCV. Since that time, however, Gen-Probe has begun distribution of its  
27 Aptima Combo 2 kits for detection of sexually transmitted disease. From a structural and  
28 theoretical perspective, both types of products perform in a similar manner. As such, any  
reference to Gen-Probe's NAT products for HIV and HCV should apply equally to Gen-Probe's  
Aptima Combo 2 products and any judgment of non-infringement should apply to those products  
as well.

1 U.S.C. § 112, paragraph 6.

2 **1. The structure and performance of Gen-Probe's NAT test kits**

3 **32.** Gen-Probe's NAT test kits incorporate an independently patented target capture  
4 methodology and a proprietary and independently patented specific amplification technique  
5 generically termed "TMA." Although numerous bases exit to distinguish Gen-Probe's products,  
6 the following contentions of fact establish that Gen-Probe's use of TMA amplification in those  
7 products singularly establishes that Gen-Probe's products do not infringe the '338 patent under the  
8 doctrine of equivalents.

9 **33.** Although Gen-Probe contends that the generic differences between TMA and the  
10 non-specific amplification techniques claimed in the '338 patent independently establish the lack  
11 of equivalence of Gen-Probe's products, the significant enhancements that Gen-Probe has  
12 designed into its practicing embodiments of TMA are particularly significant here for two reasons.  
13 To begin with, in order to satisfy its burden of proof that Gen-Probe's products infringe the '338  
14 patent, Vysis must prove that the products -- *as designed and practiced* -- infringe. Accordingly,  
15 proof that "generic" TMA cannot infringe the '338 patent is sufficient for a judgment of *non-*  
16 *infringement* in favor of Gen-Probe. However, for Vysis to sustain its burden of proof of  
17 infringement, it must show that the *particular* embodiments of TMA as practiced in Gen-Probe's  
18 accused products infringe.

19 **34.** Vysis cannot satisfy that obligation for several reasons. Fundamentally, the  
20 embodiments of TMA practiced in Gen-Probe's products represent significant refinements and  
21 advances over "generic" TMA and those differences further establish the lack of equivalence.  
22 Since the time Gen-Probe scientists invented TMA, tens of thousands of person-hours have been  
23 devoted to refining general TMA to the particular embodiment practiced in Gen-Probe's products.

24 **35.** From a procedural basis, Vysis' expert admits that he has not examined the  
25 embodiments of TMA that Gen-Probe has employed in its products nor reviewed the relevant  
26 product literature associated with those products. Because Vysis and its expert hold the burden of  
27 proof on this issue, they cannot meet that burden by reason of this fundamental lack of evidence  
28 and proof.

1           36. Gen-Probe's accused products consist of packaged kits that consist of reagents,  
2 enzymes, target capture beads and nucleic acid capture probes all specifically constructed and  
3 designed for detection of specified nucleic acid targets comprised in targeted pathogenic  
4 organisms. Pursuant to FDA regulations, Gen-Probe includes within each kit a detailed package  
5 insert that provide detailed and precise instructions for the performance of the diagnostic  
6 procedure using those constituent components.

7           37. All of the enzymes and other constituent components contained in Gen-Probe's  
8 products have non-infringing uses. Thus, as to the asserted method claims, Gen-Probe only has  
9 liability for "indirect" infringement where its customers use its kits as specifically directed in  
10 accordance with the detailed instructions contained on the package inserts.

11           2.       **Amplifying the Target Polynucleotide**

12                   a.       **Gen-Probe's TMA Method Does Not Perform Substantially The**  
13                           **Same Function as Non-specific Amplification Methods**

14           38. As mentioned above, the Court has previously construed the claims of the '338  
15 patent to encompass only non-specific amplification. Vysis has admitted that Gen-Probe's TMA  
16 products do not use non-specific amplification methods and the court has granted partial summary  
17 judgment on the issue of literal infringement. Therefore the only remaining issue in the case is  
18 whether Gen-Probe's blood screening assay infringes the '338 patent under the doctrine of  
19 equivalent. Gen-Probe denies such infringement. There are substantial differences between Gen-  
20 Probe's TMA method and the non-specific amplification methods described and claimed in the  
21 '338 patent, when considered as separate elements and when considered in the "context of the  
22 claims" under the "all elements rule." TMA does not perform substantially the same function in  
23 substantially the same way to achieve substantially the same result as the non-specific methods of  
24 amplification encompassed by the claims of the '338 patent.

25           39. Specific amplification techniques, in general, and TMA in particular, function much  
26 differently than do non-specific amplification techniques. Gen-Probe's TMA amplification  
27 method, like other specific amplification techniques such as the Polymerase Chain Reaction  
28 ("PCR"), uses specific primers that attach to carefully selected portions (or "sequences") of the

1 target organism's nucleic acids. These sequence-specific primers are carefully researched and  
2 designed to attach to unique nucleic acid sequences of the target organism, so that the test  
3 produces accurate results. Non-specific amplification methods use "random" primers rather than  
4 "specific" primers.

5       **40.** Gen-Probe's TMA method functions to exponentially increase both the *absolute*  
6 and *relative* amounts of a particular nucleic acid sequence of interest in a mixture of nucleic acids.  
7 In direct contrast, non-specific amplification functions only to increase the absolute amount of *all*  
8 nucleic acids present in a sample and does *not* increase the relative amount of a particular nucleic  
9 acid sequence of interest.

10       **41.** Specific amplification is useful for diagnostic purposes even without a target  
11 capture step. In contrast, non-specific amplification is *not* a viable diagnostic method because it  
12 does not increase the amount of a target nucleic acid relative to other nucleic acid sequences.

13                   **b. Gen-Probe's TMA Method Does Not Perform In Substantially**  
14                   **The Same Way as Non-specific Amplification Methods**

15       **42.** The enzymes and primers used in any amplification process can be specific or non-  
16 specific. The primers used in Gen-Probe's specific TMA amplification method have been carefully  
17 selected by Gen-Probe's scientists and are generally designed to bind to specific, unique sequences  
18 in a DNA or RNA molecule. In amplification processes, sequence-specific primers and enzymes  
19 such as those used in TMA play a role substantially different from non-specific primers and  
20 enzymes. This fact is well known to those of ordinary skill in the art. For example, specific  
21 primers and enzymes can function together to amplify a target nucleic acid only if the specific  
22 sequence of interest bound by the primer and/or recognized by the enzyme is present in the  
23 sample.

24       **43.** By contrast, non-specific primers and enzymes will amplify *any* and *all* sequences  
25 present in the sample. The random primers will potentially bind to all of the sequences in the  
26 sample and non-specific replication enzymes will catalyze DNA or RNA synthesis at points  
27 throughout the entire lengths of the nucleic acid molecules present without regard to sequence.

28       **44.** In its TMA method, Gen-Probe uses two amplification enzymes that depend upon

1 the presence of specific primers. One of these enzymes is reverse transcriptase ("RT"). RT is a  
2 DNA polymerase that produces a complementary DNA strand copy of a single-stranded RNA or  
3 DNA that has a bound primer. In TMA, RT produces complementary DNA from the target  
4 nucleic acids (or their complementary strands) only if the sequence-specific primers first bind to a  
5 single strand of RNA or DNA. That is, if the target organism is not present in the sample, the  
6 primers will be unable to bind to the target sequence and the RT will not initiate synthesis.

7       45. Another specific primer used in Gen-Probe's method includes a specific "promoter"  
8 sequence that is recognized by another enzyme ("T7 RNA polymerase") that binds specifically to  
9 that promoter sequence to produce many RNA copies by transcription<sup>2</sup>. A functional "T7  
10 promoter" is formed in the course of the TMA process if, and only if, (1) the primer finds and  
11 binds to its complementary target sequence in the captured target molecule so that the target  
12 sequence is copied by reverse transcriptase and (2) the second primer binds to the newly  
13 synthesized DNA and DNA polymerase makes the complementary DNA strand. If this double-  
14 stranded, and hence functional, T7 promoter is formed as a result of these two primer binding and  
15 extension processes, then the T7 RNA polymerase used in Gen-Probe's HIV/HCV test will  
16 amplify the sequence attached to the T7 promoter sequence. Significantly, the T7 RNA  
17 polymerase does not amplify other sequences present in the sample because they are not attached  
18 to a T7 promoter sequence.

19       46. In Gen-Probe's HIV/HCV test, the T7 polymerase enzyme *specifically* recognizes  
20 the T7 promoter sequence, which has been *specifically* attached to the target sequence by the  
21 binding and replication of *specific* primers, and the T7 polymerase *specifically* amplifies the target  
22 sequence starting only from that T7 promoter sequence. The process repeats in a cyclic fashion,  
23 amplifying the particular target sequence of interest. Gen-Probe's amplification method therefore  
24 safeguards against amplification of non-target sequences and thus protects against false positive  
25 results. In contrast, non-specific amplification methods amplify all sequences in the sample. Thus,  
26 TMA functions in a way that is substantially different than the way in which non-specific

27  
28 <sup>2</sup> "Transcription" is the process of making single-stranded RNA copies of sequences present in a  
strand of DNA.

1 amplification functions.

2 c. **Gen-Probe's TMA Method Does Not Produce Substantially The**  
3 **Same Results as Non-specific Amplification Methods**

4 47. The results obtained from Gen-Probe's method are also substantially different than  
5 the results achieved by non-specific amplification methods.

6 48. First, specific amplification methods result in the increase in a particular nucleic  
7 acid sequence, in both *absolute* and *relative* terms. On the other hand, non-specific amplification  
8 does not achieve an increase in the amount of a particular nucleic acid relative to other nucleic  
9 acids present in the sample. Instead, non-specific amplification increases the absolute amount of  
10 all nucleic acids present in the reaction mixture.

11 49. Second, specific amplification methods commonly achieve *exponential*  
12 amplification of the target sequence, as compared with linear amplification. Sustained, significant,  
13 exponential amplification is a hallmark of specific amplification methods. In contrast, the non-  
14 specific amplification methods described in the '338 patent achieve only linear amplification, not  
15 exponential amplification. For example, because random primers bind at various places along the  
16 nucleic acids present in the sample, the products of amplification are generally fragmented and  
17 may or may not include the sequence to be detected. If these products were then subjected to  
18 another round of non-specific amplification, the resulting products would be smaller still. Multiple  
19 rounds of non-specific amplification thus diminish rapidly in efficiency, whereas multiple rounds  
20 of specific amplification produce extraordinarily large amounts of the isolated full size product  
21 nucleic acids in very short periods of time.

22 50. Third, non-specific amplification using random hexamer primers results in  
23 fragmented nucleic acids, each of which contains the random sequences present in the random  
24 primers. The resulting products are thus heterogeneous and have undefined composition. Such  
25 nucleic acids are unsuitable for most of the purposes for which homogeneous, specifically  
26 amplified nucleic acids of known composition are employed. As a result, Gen-Probe's TMA  
27 method also does not yield the same result as that obtained with non-specific amplification.

1           51. The inventors and other employees of Gene-Trak/Vysis admitted that the non-  
2 specific methods of amplification disclosed in the specification of the '338 patent were "different"  
3 from specific amplification methods and further admitted that non-specific amplification was the  
4 "opposite" of specific amplification methods such as TMA. The text of the '338 patent  
5 specification itself admits and highlights the differences between the two methods of  
6 amplification.

7           **E. THE '338 PATENT IS INVALID**

8           52. The claims of the '338 patent are invalid by reason of one or more provisions of  
9 Title 35 of the United States Code.

10           **1. Lack of Enablement Under 35 U.S.C. §112, ¶1**

11           53. Vysis contends that the relevant disclosure for the '338 patent was filed on  
12 December 21, 1987. In the specification, the inventors disclosed three preferred embodiments,  
13 Examples 1 through 3, that show *only* the use of target capture without amplification. In the  
14 remaining four preferred embodiments, Examples 4 through 7, the inventors purport to disclose the  
15 combination of target capture followed by non-specific amplification techniques.

16           54. In Example 4, the inventors set forth an embodiment of their claimed methods that  
17 describes the use of *E. coli* RNA polymerase lacking sigma subunit, i.e., core enzyme. The sigma  
18 subunit is removed according to known procedures, but the '338 patent states that "other phage or  
19 bacterial RNA polymerases that lack transcriptional specificity can also be used." ('338 patent,  
20 col. 30:64-31:1.) The core enzyme is added to a nucleotide triphosphate/transcription buffer  
21 solution and the resulting non-specific transcription of the target DNA produces RNA transcripts  
22 of the target DNA, which are then captured using a capture probe that is homologous to a sequence  
23 of the RNA transcripts. The inventors describe the use of a reporter probe for detection. Example  
24 4 describes a process that is known as "linear amplification."

25           55. In Example 5, the inventors describe the use of universal or random primers  
26 comprising random nucleotide sequences of short DNA fragments averaging about 6 nucleotides  
27 in length to prime or initiate DNA synthesis. These short sequences are known as "random  
28 hexamers" and their complementary sequences frequently occur within virtually all nucleic acids.



1 As a population, the random primers tend to hybridize at multiple points along any nucleic acid  
2 sequence even though each individual primer binds to its complementary sequence. In the  
3 presence of polymerase enzymes used to replicate and synthesize nucleic acids the binding of the  
4 random primers will initiate synthesis of complementary DNA sequences to form double-stranded  
5 DNA that in turn can be used as a template for the use of still further non-specific enzymes to  
6 make multiple copies (RNA transcripts) of any nucleic acids in the sample. In Example 5, the  
7 inventors describe the use of RNA polymerase lacking sigma subunit to make these transcripts. In  
8 a parenthetical statement in Example 5, the inventors say that a capture probe could be used to  
9 make the double-stranded DNA, followed by non-specific transcription. Example 5 describes, in  
10 all embodiments, a linear, non-specific amplification process.

11 56. Vysis has admitted during discovery that it never attempted to practice the methods  
12 described in Examples 4 and 5. Vysis never actually reduced to practice the inventions described  
13 in Examples 4 and 5. Significant information that would be needed to enable one skilled in the art  
14 to practice linear amplification is omitted from Examples 4 and 5. The linear, non-specific  
15 amplification methods of Examples 4 and 5 are not enabled by the disclosures of the '338 patent's  
16 specification.

17 57. Amplification methods may be linear or exponential. Exponential amplification is  
18 entirely different from linear amplification. Exponential amplification can be thought of as a  
19 process of making copies of copies, *i.e.* the amplification products themselves are further  
20 amplified, resulting in a geometric increase in the amount of the products. In contrast, linear  
21 amplification can be described as making one copy at a time from the same original template.  
22 Linear amplification differs substantially from exponential amplification in that in linear  
23 amplification techniques copies are not made from copies. Rather, copies are only made  
24 individually from the original target nucleic acid sequences, or a double-stranded template made  
25 from the target nucleic acid. Thus, after one cycle you have one copy, after two cycles, you will  
26 have two copies, and so on.

27 58. One of the significant advancements in molecular biology was the invention of the  
28 polymerase chain reaction ("PCR") method of nucleic acid amplification. This method permitted

1 exponential amplification of a specific target sequence. Following the announcement of the PCR  
2 method in 1985, those skilled in the art distinguished between linear amplification and exponential  
3 amplification methods. TMA is an exponential amplification method.

4       **59.** One of ordinary skill in the art would not only recognize the substantial differences  
5 in the function and way that exponential techniques work when compared to linear techniques, but  
6 one of ordinary skill would also recognize that substantial differences exist in the result and utility  
7 of the two techniques. The linear amplification techniques would require more "target" to be  
8 present in a sample as well as more time to have a reasonable chance of ultimately being able to  
9 detect or measure any amplification products above background levels. Exponential amplification  
10 is substantially different. Exponential amplification requires much less target to be present in the  
11 sample (i.e., because even one instance of the target can rapidly be multiplied) and less time to  
12 yield sufficient copies to permit detecting/measuring the amplification products above background  
13 levels. For this reason, exponential amplification is much more suitable for use in diagnostic  
14 applications because it results in more copies of the target nucleotide being made available over  
15 the same time. Thus, in a diagnostic application, a scientist can begin with much less target  
16 material and spend less time to produce an appropriate level of target for detection. This makes  
17 exponential amplification far more practical for use in diagnostics than linear amplification.  
18 Methods of linear amplification did not offer the advantages of exponential amplification and  
19 could not compete with PCR or TMA for routine use in amplified clinical assays.

20       **60.** The claims of the '338 patent encompass both non-specific linear and non-specific  
21 exponential amplification. Examples 4 and 5 purport to describe methods of linear amplification  
22 only. Neither Example 4 or 5 describe a method by which exponential amplification of the target  
23 polynucleotide can be achieved. Hence, Examples 4 and 5 are not enabling of the invention as  
24 broadly as it is claimed.

25       **61.** In Example 6, the inventors set forth an embodiment of their claimed methods that  
26 describes the use of "random" primers and cycles of heating. The patent does not state whether the  
27 exemplified process is linear or exponential; however, Vysis has belatedly asserted that the process  
28 of Example 6 will allow exponential amplification of a target DNA sequence. As the specification

provides, the random primers are six-base oligonucleotides constructed such that the bases at each nucleotide position are constructed in random sequence. As a matter of statistical variation, some of the random primers can be expected to bind to any polynucleotide present in a sample. Following that non-specific binding, a standard DNA polymerase, Klenow fragment, is then used to form double-stranded DNA from the original polynucleotide. The double-stranded DNA is then heated resulting in a physical separation of the double-stranded DNA into its two complementary single strands of DNA (i.e., the original strand and its complementary strand). Once separated into two strands, the process of creating doubled-stranded DNA from each single strand is repeated about 10 times using random primers and additional DNA polymerase. According to the '338 patent, the process would result in 1000-fold increase in the level of target DNA. (Col. 32, lines 2-5.)

62. In Example 7, the inventors described the apparent use of a natural enzyme, Q $\beta$  replicase, to nonspecifically amplify target RNA. According to this example, transcripts or alternatively, ribosomal RNA ("rRNA"), are first captured, and then RNA complementary to the captured RNA is synthesized. The specification then states that the Q $\beta$  replicase enzyme could be used to make copies of the target RNA exponentially. However, the specification does not provide any detail as to the method by which one would accomplish that technique. Rather, it merely suggests that the procedure disclosed in a paper authored by Thomas Blumenthal in 1980 would allow the claimed exponential amplification of the target polynucleotides.

a. **Example 6 was never successfully practiced by Vysis or its predecessor, Gene-Trak.**

63. To the extent that the inventors' disclosure of Example 6 in prophetic format suggests that they had not attempted to reduce that technique to practice by the filing date of December 21, 1987, Gene Trak's internal records show otherwise. To the contrary, Gene Trak's internal records show that Gene Trak's designated "amplification group" undertook a dedicated project with the express object to successfully implement nucleic acid amplification using random primers.

64. Gene Trak's amplification group initiated that project in July 1987. That group was

1 staffed by skilled scientists who reported directly and indirectly to senior scientists and managers  
2 at Gene Trak, including Jonathan Lawrie, one of the named inventors of the '338 patent. One of  
3 the amplification group's stated goals was to reduce to practice the technique for non-specific  
4 amplification using random primers as set forth in Example 6.

5 65. Using more elaborate experimental details and techniques than those disclosed in  
6 Example 6, Gene Trak's amplification group struggled for at least 5 months attempting to non-  
7 specifically amplify a target nucleic acid with random primers. They never succeeded. Indeed,  
8 rather than *amplify* the target, the results of their efforts resulted in a *net reduction* in target.  
9 Eventually, the amplification group at Gene Trak abandoned their efforts.

10 66. In their unsuccessful effort to reduce the technique disclosed in Example 6 to  
11 practice, Gene Trak's team made a number of observations that bear upon the issue of enablement.  
12 Most significantly, they concluded that amplification using random primers was "impractical for  
13 exploitation as an amplification scheme," and "of limited use for target amplification." Second,  
14 they also found that the technique was also "very sensitive to perturbation, that is, changes in  
15 experimental condition such as primer concentration."

16 67. Neither Gene-Trak nor Vysis ever successfully performed the technique disclosed  
17 in Example 6. Thus, the method of Example 6 was never actually reduced to practice.

18 68. Gene Trak's failure to practice the technique of Example 6 was predictable and  
19 inevitable. As Gene Trak's team discovered, *any* technique using non-specific amplification with  
20 random primers is subject to significant perturbation which therefore requires an inordinate  
21 amount of experimentation to implement—the details of which are not disclosed in the  
22 specification.

23 69. The experimental details required to practice non-specific amplification methods  
24 using random primers was separately patented in August 1991 by James Hartley and later in April  
25 1992 by Dr. Hartley and another scientist, Mark S. Berninger. The details disclosed in their  
26 patents, United States Patent Nos. 5,043,272 and 5,106,727, respectively, dramatically contrast the  
27 experimental details necessary to practice random priming amplification with the limited  
28 disclosures of the specification of the '338 patent.

1           70. As Gene Trak's investigators discovered, the technique for random priming  
2 amplification requires extensive work to determine the reaction conditions and parameters that will  
3 allow amplification to occur. The details of these conditions are missing from the '338 patent  
4 disclosure. For instance, Example 6 purports to use a particular DNA polymerase, Klenow  
5 fragment, but Example 6 does not specify the amount of this enzyme that should be used.  
6 Furthermore, the concentration of primers and the incubation times and temperatures for DNA  
7 synthesis are also not disclosed in Example 6. Similarly, although Example 6 purports to use  
8 certain reactants such as deoxynucleotide triphosphates ("dNTP's") as part of the reaction, Example  
9 6 does not specify the amount of these components. Furthermore, Example 6 directs the use of  
10 "appropriate buffer," but does not specify the components or concentration to be used.<sup>3</sup>

11           71. The experimental parameters for each of the foregoing conditions and components  
12 for random primer amplification are critical to the successful practice of amplification using  
13 random primers. As evidenced by the unsuccessful efforts of Gene Trak, as of December 21,  
14 1987, one of ordinary skill in nucleic acid amplification would not have been able to determine the  
15 necessary parameters and techniques for random priming amplification from Example 6 without  
16 undue and significant experimentation. Indeed, as of the filing date, there was no published data  
17 or technique that would even suggest that *any* technique for amplification using random primers  
18 could succeed on any basis to believe that the skeletal details provided in Example 6 would enable  
19 exponential amplification of a target nucleic acid.

20           **b. Neither Gene Trak nor Vysis ever attempted the technique**  
21           **disclosed in Example 7.**

22           72. Example 7 purports to describe non-specific amplification of target nucleic acids  
23 using an RNA polymerase known as Q $\beta$  replicase. With the limited disclosure of Example 7, the  
24 inventors claimed that one could obtain exponential amplification of any target nucleic acid.

25           73. Q $\beta$  replicase is a naturally occurring enzyme that is derived from bacteria infected

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26           <sup>3</sup> With respect to the buffer prescribed for use in Example 6, it is not at all clear what the  
27 composition and concentrations the inventors intended. Even if one were to assume that the buffer  
28 described in Example 5 were to be used, however, the disclosure of the buffer described in  
Example 5 lacks still further information concerning the concentration of Klenow polymerase, the  
concentration of hexamer primers, and the times and temperature of incubation.

1 by a virus known as Q $\beta$ . As of 1987, Q $\beta$  replicase was known to have extraordinary specificity  
2 that prevented it from copying nucleic acids other than Q $\beta$  genomic RNA. In other words, the Q $\beta$   
3 replicase enzyme will not naturally copy or amplify target nucleic acids other than the specific  
4 sequence of Q $\beta$  genomic RNA.

5 74. Contrasted with the extensive, albeit unsuccessful, efforts of Gene Trak scientists to  
6 practice Example 6, as of the filing date of the '338 patent, Gene Trak scientists never attempted to  
7 implement the technique of Example 7. To this date, neither Gene Trak nor Vysis scientists have  
8 ever attempted to perform the technique disclosed in Example 7. Thus, the method of Example 7  
9 was never actually reduced to practice.

10 **c. The Disclosure of Example 7 is also deficient.**

11 75. The likely reason for Gene Trak's failure to attempt Example 7 is directly  
12 attributable to the absence of any disclosure of the experimental details necessary to obtain non-  
13 specific amplification of target nucleic acids with Q $\beta$  replicase. The full extent of the disclosure  
14 provided in Example 7 is the suggestion to follow a procedure set forth in a 1980 publication by  
15 Thomas Blumenthal.

16 76. At best, in 1980, Thomas Blumenthal published the results of experiments in which  
17 he obtained fragmentary, partial transcription copies of 3 synthetic and 2 naturally occurring RNA  
18 molecules. He reported that he obtained that success through extensive experimentation that  
19 resulted in wide variances between the reaction conditions necessary to transcribe each of the  
20 target RNAs. Significantly, his results showed that the reaction conditions for each different target  
21 nucleic acid differed appreciably and, most importantly, unpredictably for each different target  
22 nucleic acid. As such, a mere reference to Blumenthal's paper would not provide sufficient detail  
23 to enable skilled scientists to amplify any given target nucleic acid without undue experimentation.

24 77. Another equally significant problem with the reliance on Blumenthal's study lies in  
25 the fact that it only attempted to obtain a single, complementary transcript copy of each target  
26 nucleic acid. Upon conclusion of the reaction described by Blumenthal, the complementary  
27 transcript copy of the target RNA remains coupled to the target thereby rendering both the target  
28 and the complementary copy unavailable for further copying by Q $\beta$ . The entire process results in

1 the creation of only one additional complementary nucleic acid for each target molecule. Thus,  
2 even if a complementary transcript copy was successfully synthesized, the Blumenthal technique  
3 results in a termination of the reaction upon creation of that complementary transcript. Such a  
4 result – the creation of a single complementary copy per target molecule is not “amplification” of  
5 the target.

6 78. Moreover, Example 7 of the ‘338 patent purports to teach a method of *exponential*  
7 amplification of target nucleic acids using Q $\beta$  replicase whereby template products are created and  
8 used to make still further amplified target molecules. Blumenthal’s paper only showed limited  
9 success in the linear production of fragmentary portions of a few selected nucleic acids. As of  
10 1987, not even Blumenthal had achieved success in using Q $\beta$  replicase to obtain the claimed  
11 exponential amplification of target molecules. Thus, in 1987, no methods were known in which  
12 Q $\beta$  replicase could be used to exponentially amplify target nucleic acids.

13 79. Accordingly, the evidence of “enablement” of Example 7 is equally lacking. There  
14 was no scientific knowledge in 1987 that would allow a person of ordinary skill to perform  
15 exponential target amplification using the enzyme Q $\beta$  replicase. The minimal disclosure of  
16 Example 7 certainly did not provide the missing information. Even as to linear amplification using  
17 Q $\beta$  replicase, the only evidence supporting that technique showed that the conditions necessary to  
18 transcribe fragments of selected target nucleic acids varied unpredictably, thus requiring an  
19 extraordinary amount of experimentation to achieve if at all possible.

20 80. Thus, in each of the two preferred embodiments claimed to disclose exponential  
21 non-specific amplification, Examples 6 and 7, Gene Trak did not and could not enable either linear  
22 or exponential amplification using the techniques disclosed in those embodiments. Examples 4  
23 and 5 disclose only linear amplification, and they, too, were never actually reduced to practice.

24 **2. Obviousness, Anticipation, and Prior Public Disclosure Under 35 U.S.C.**  
25 **§§102, 103**

26 **a. The priority date of the ‘338 patent is no earlier than January**  
27 **31, 1991.**

28 81. Vysis asserts that the claims of the ‘338 patent are entitled to a December 1987  
priority date. However, for a multiple of prosecution irregularities committed by Vysis and its

1 predecessors in the prosecution of the '338 patent, Vysis is not entitled to that claimed priority  
2 date.

3 **82.** On October 23, 1986, the applicants filed a patent application entitled "Target and  
4 Background Capture Methods and Apparatus for Affinity Assays." After filing, the Patent Office  
5 assigned that application the numerical designation, Serial No. 06/922,155 (the "'155  
6 application"). Although, the '155 application purported to describe a technique for reversible  
7 target capture, it contained no disclosure of or claims to amplification techniques as claimed by  
8 Vysis in the '338 patent. The application identified Mark L. Collins as the sole inventor of the  
9 alleged inventions claimed in the '155 application.

10 **83.** On December 21, 1987, prior to substantive examination of the '155 application by  
11 the Patent Office, Vysis filed a Continuation-in-Part of the '155 application. The Patent Office  
12 assigned this Continuation-in-Part application Serial No. 07/136,920 (the "'920 application"). The  
13 applicants entitled the '920 application "Target and Background Capture Methods with  
14 Amplification," and initially submitted claims in the '920 application to methods of nucleic acid  
15 capture and amplification (claims 1-23), and a claim to an instrument for performing assays for  
16 target polynucleotides (claim 24).

17 **84.** In its initial examination of the '920 application, the Patent Office issued a  
18 restriction requirement because it deemed the claimed inventions of capture and amplification  
19 claims and the instrument claims of the '920 application as distinct. In response to that restriction  
20 requirement, the applicants elected to proceed in the '920 application by prosecuting only the  
21 method claims (claims 1-23).

22 **85.** On July 20, 1990, following the applicants' election to proceed with only the  
23 method claims in the '920 application, the Patent Office issued an office action regarding that  
24 application by which it rejected all claims of the '920 application on prior art and other grounds of  
25 patentability. The Patent Office provided the applicants until October 20, 1990, with extensions  
26 available until January 20, 1991, to submit a substantive response to that office action.

27 **86.** Rather than prepare a substantive response to the July 20, 1990 office action, and in  
28 order to continue prosecuting claims to methods of nucleic acid capture and amplification, on



1 January 22, 1991, the applicants filed a continuation application from the '920 application. The  
2 Patent Office designated this continuation application as application Serial No. 07/644,967 (the  
3 "'967 application"). The '920 application became abandoned as of midnight, January 22, 1991  
4 pursuant to 35 U.S.C. § 133.

5 87. On March 12, 1991, the Patent Office issued an office action for the '967  
6 application by which it issued a final rejection of all claims in that application. Pursuant to statute,  
7 the Patent Office provided the applicants with a shortened response period until June 12, 1992 to  
8 respond to this final rejection of the claims of the '967 application.

9 88. The '967 application became abandoned as of midnight, June 12, 1992 pursuant to  
10 35 U.S.C. § 133. On September 24, 1992, Vysis filed a petition to revive the '967 application  
11 through September 14, 1992, the date to which it could have automatically obtained an extension  
12 of time by paying a fee. The PTO granted Vysis's petition to revive the '967 so that it would  
13 become abandoned as of midnight, September 14, 1992 (rather than remain abandoned as of  
14 midnight June 12, 1992).

15 89. Rather than prepare a substantive response to the March 12, 1992, office action, and  
16 in order to continue prosecuting claims to methods of nucleic acid capture and amplification, on  
17 September 14, 1992, the applicants filed a continuation application to the '967 application. (At that  
18 time the prior '967 application was abandoned, but it was revived as set forth above.) The Patent  
19 Office designated this further continuation application Serial No. 07/944,505 (the "'505  
20 application"). Consistent with continuation practice and rules, the applicants presented only  
21 claims to methods of nucleic acid capture and amplification in the '505 application, the  
22 instrument-related claim having been withdrawn by prior election.

23 90. The '505 application became abandoned as of midnight, February 5, 1993 pursuant  
24 to 35 U.S.C. § 133. Following the PTO's rejection of all claims in the '505 application, Vysis took  
25 no action with respect to the '505 application for approximately one year and six months, until  
26 May 3, 1994.

27 91. On November 5, 1992, the Patent Office issued an office action for the '505  
28 application by which it issued a final rejection of the claims submitted with that application.

Pursuant to statute, the Patent Office provided the applicants with a shortened response period until February 5, 1993 to respond to this final rejection of the claims of the '505 application. Applicants' counsel received this office action and his staff docketed the deadlines for response.

92. With the applicants' express knowledge and awareness of the requirement to respond to the November 5, 1992 office action within the statutorily required time and the further knowledge of the consequences of abandonment arising from any failure to respond within that required time, applicants intentionally elected not to respond to the office action.

93. Consistent with Patent Office rules and procedures, following the applicants' failure to respond to the November 5, 1992 office action, on June 16, 1993, the Patent Office sent a formal notice of abandonment of the '505 application to the applicants. Applicants' counsel received this notice of abandonment and his staff docketed the deadlines for response. However, consistent with the applicants' intentional decision not to respond to the office action, the applicants intentionally determined not to respond to the notice of abandonment.

### **3. Facts Related to the Prosecution of the Alleged Instrument Invention**

94. The applicants intentionally failed to respond to the November 5, 1992, office action rejecting the claims of the '505 application and further intentionally failed to respond to the June 16, 1993 notice of abandonment as a result of their decision to abandon the alleged invention directed to methods of nucleic acid capture and amplification originally elected for prosecution in the '920, '967 and '505 applications.

95. On January 31, 1991, consistent with the applicants' decision to acquiesce to the Patent Office's July 20, 1990 restriction requirement issued with respect to the distinct claimed inventions that applicants presented in the '920 application, the applicants filed a separate application by which they elected to prosecute only instrument-related claims. The Patent Office assigned this instrument application Serial No. 07/648,468 (the "'468 application"). As originally filed (and consistent with their election in response to the restriction requirement imposed in the '920 application), the applicants submitted only claims directed to an instrument for performing assays for target polynucleotides. The applicants entitled the '468 application "Closed Vessel for Isolating Target Molecules and for Performing Amplification." The '468 application claimed four

1 inventors, only one of whom was an inventor on the '967 application. From the time of its filing in  
2 January 1991 until July 1, 1999, the '468 application directly claimed the benefit of the filing date  
3 of the '920 application.

4 96. Through the '468 application, the applicants claimed priority of their instrument  
5 invention as a continuation-in-part application to the '920 and earlier '155 applications. This  
6 claim of priority resulted from the deliberate and intentional choice of counsel for the applicants.  
7 However, applicants' claim to priority to the '920 and '155 applications was defective under 35  
8 U.S.C. § 120 for several reasons.

9 97. First, in order to claim priority to a prior application, at least three requirements  
10 must be met: 1) there must be co-pendency with the prior application; (2) there must be continuity  
11 of invention and 3) there must be at least one inventor of common subject matter between the two  
12 inventions.

13 98. The element of co-pendency required that the '468 application have been filed prior  
14 to the abandonment of the priority applications. In this case, although the applicants filed the '468  
15 application on January 31, 1991, they had intentionally abandoned the '920 application on January  
16 22, 1991 and intentionally abandoned the '155 application on February 3, 1990. Applicants and  
17 their counsel intentionally failed to disclose this lack of co-pendency of the '468 application during  
18 the prosecution of the '468 application. Due to the lack of co-pendency, the earliest date to which  
19 the '468 patent could claim priority under Section 120 was its own filing date of January 31, 1991.  
20 (As of this date, a PCT counterpart application to the applications for the method ultimately  
21 disclosed '338 patent had already been published and such publication established a statutory bar  
22 to any claims in the United States for similar inventions.)

23 99. Even ignoring the defective claim of co-pendency, the requirement of Section 120  
24 for a common inventor provides continuity only as to that subject matter contributed by the  
25 common inventor. In this case, the only common inventor was Mark Collins. In deposition  
26 testimony in this case, Dr. Collins admitted that his sole contribution to the '920 application (and  
27 the '338 patent) related to the process of target capture (as embodied in steps (a) and (b) of Claim  
28 1 of the '338 patent). Thus, at most, the only subject matter that was "carried forward" into the

1 '468 application was the concept of target capture to the extent embodied in the disclosure and  
2 claims of the '468 application.

3 100. In their claim of priority to the '920 and '155 applications, the applicants did not  
4 disclose the limited nature of the contribution provided by Mark Collins to the inventions claimed  
5 therein. Although that lack of disclosure may not have been material to the prosecution of the '468  
6 application per se, it is extremely relevant to later stages of the prosecution of the '338 patent.

7 101. The Patent Office initially rejected all the claims of the '468 application on prior art  
8 and other grounds of patentability in an office action mailed March 18, 1992. The Patent Office  
9 provided the applicants until June 18, 1992 to submit a substantive response to that office action.

10 102. Rather than prepare a substantive response to the March 18, 1992 office action, and  
11 in order to continue prosecuting claims to an instrument for performing assays for target  
12 polynucleotides, on September 17, 1992, the applicants filed a continuation application from the  
13 '468 application. The Patent Office designated this continuation application as application Serial  
14 No. 07/946,749 (the "'749 application"). Consistent with the restriction requirement originally  
15 issued in the '920 application, the applicants submitted only claims directed to an instrument for  
16 performing assays for target polynucleotides in the '749 application. The '468 application was  
17 abandoned as of midnight, September 18, 1992.

18 103. The Patent Office initially rejected all the claims of the '749 application on prior art  
19 and other grounds of patentability in an office action mailed March 22, 1993. The Patent Office  
20 provided the applicants until June 22, 1993 to submit a substantive response to that office action.  
21 In rejecting the '749 application, the PTO recognized that:

22 the present application does not receive benefit of the filing date of  
23 06/922155 and 07/136920. The prior applications, 06/922155 and  
24 07/136920, fail to disclose or suggest the present invention. The  
25 continuity between the present application and the other appear only  
to be in the area of amplification rather than in the scope of the  
invention. The present application is therefore believed to only have  
benefit of the filing date, 1/31/1991, of 07/648468.

26 (March 22, 1993 office action at page 2, lines 1-10.

27 104. Rather than prepare a substantive response to the March 22, 1993 office action, and  
28 in order to continue prosecuting claims to an instrument for performing assays for target

1 polynucleotides, on September 21, 1993, the applicants filed a continuation application from the  
2 '749 application. The Patent Office designated this continuation application as application Serial  
3 No. 08/124,826 (the "'826 application"). Consistent with the restriction requirement originally  
4 issued in the '920 application, the applicants submitted only claims directed to an instrument for  
5 performing assays for target polynucleotides in the '826 application. The '749 application was  
6 abandoned as of midnight, September 22, 1993.

7       **105.** The Patent Office initially and finally rejected all the claims of the '826 application  
8 on prior art and other grounds of patentability in an office action mailed December 9, 1993. The  
9 Patent Office provided the applicants until March 9, 1994 to submit a substantive response to that  
10 office action. In rejecting the '826 application, the PTO recognized that the application did not  
11 receive the benefit of the filing date of the '155 and '920 applications because those prior  
12 applications failed to disclose or suggest the invention claimed in the '468, 749, and '826  
13 applications.

14       **106.** Rather than prepare a substantive response to the December 9, 1993 office action,  
15 and in order to continue prosecuting claims to an instrument for performing assays for target  
16 polynucleotides, on June 8, 1994, the applicants filed a continuation application from the '826  
17 application. The Patent Office designated this continuation application as application Serial No.  
18 08/257,469 (the "'469 application"). Consistent with the restriction requirement originally issued  
19 in the '920 application, the applicants submitted only claims directed to an instrument for  
20 performing assays for target polynucleotides in the '469 application. The '826 application was  
21 abandoned as of midnight, June 9, 1994.

22       **107.** The Patent Office initially and finally rejected all the claims of the '469 application  
23 on prior art and other grounds of patentability in an office action mailed September 12, 1994. The  
24 Patent Office provided the applicants until December 12, 1994 to submit a substantive response to  
25 that office action. In rejecting the '469 application, the PTO recognized that the application did  
26 not receive the benefit of the filing date of the '155 and '920 applications because those prior  
27 applications failed to disclose or suggest the invention claimed in the '468, 749, '826, and '469  
28 applications.

1           **108.** Rather than prepare a substantive response to the December 12, 1994 office action,  
2 and in order to continue prosecuting claims to an instrument for performing assays for target  
3 polynucleotides, on March 8, 1995, the applicants filed a continuation application from the '469  
4 application. The Patent Office designated this continuation application as application Serial No.  
5 08/400,657 (the "'657 application"). Consistent with the restriction requirement originally issued  
6 in the '920 application, the applicants submitted only claims directed to an instrument for  
7 performing assays for target polynucleotides in the '657 application. The '469 application was  
8 abandoned as of midnight, March 13, 1995.

9           **109.** The Patent Office initially and finally rejected all the claims of the '657 application  
10 on prior art and other grounds of patentability in an office action mailed April 25, 1995. The Patent  
11 Office provided the applicants until July 5, 1995 to submit a substantive response to that office  
12 action. In rejecting the '657 application, the PTO recognized that the application did not receive  
13 the benefit of the filing date of the '155 and '920 applications because those prior applications  
14 failed to disclose or suggest the invention claimed in the '468, 749, '826, '469, and '657  
15 applications.

16           **110.** Rather than prepare a substantive response to the April 25, 1995 office action, on  
17 October 25, 1995, the applicants submitted a notice of appeal of the '657 application. Rather than  
18 file an appeal brief, and in order to continue prosecuting claims to an instrument for performing  
19 assays for target polynucleotides, on March 25, 1996, the applicants filed a continuation  
20 application from the '657 application. The Patent Office designated this continuation application  
21 as application Serial No. 08/622,491 (the "'491 application"). Consistent with the restriction  
22 requirement originally issued in the '920 application, the applicants submitted only claims directed  
23 to an instrument for performing assays for target polynucleotides in the '491 application. The '657  
24 application was abandoned as of midnight, March 25, 1996.

25           **4. Applicants' Efforts to Overcome their Intentional Abandonment of the**  
26           **'505 Application and their Alleged Claims to Methods of Nucleic Acid**  
27           **Capture and Amplification**

28           **111.** Sometime prior to May 3, 1994, the applicants determined to attempt to reverse  
their prior intentional abandonment of the alleged invention directed to methods of nucleic acid

1 capture and amplification. As a result of that determination, on May 3, 1994, fifteen months after  
2 they failed to respond to the office action of November 5, 1993 and almost eleven months after  
3 they further failed to respond to the formal notice of abandonment, applicants attempted to revive  
4 their '505 application by filing a formal petition to revive the '505 application. In that petition, the  
5 applicants misrepresented the fact concerning their prior intentional abandonment of the '505  
6 application and claimed that they "unintentionally" failed to respond to the Patent Office. The  
7 applicants stated that "[t]he abandonment occurred as a result of the oversight of Applicants  
8 representative and was not intended by Applicants."

9       **112.** As set forth above, the applicants' claim of unintentional abandonment of the '505  
10 was false. Rather, the applicants' failure to respond to the Patent Office's rejection of the claims  
11 of '505 application directed to the claimed invention of a method of nuclei acid amplification was  
12 intentional. Indeed, the applicants' intentional decision not to respond to the '505 office action  
13 was consistent with and driven by applicants' underlying decision to abandon the invention  
14 claimed in the '505 application.

15       **113.** On October 27, 1994, the Patent Office rendered a decision denying the applicants'  
16 petition to revive the '505 application. As the Patent Office explained, the '505 application  
17 became abandoned on February 6, 1993, when the applicants failed to respond to the office action  
18 of November 5, 1992. Because the petition to revive the '505 application was filed more than one  
19 year after the '505 application became abandoned, the petition was barred under 37 C.F.R.  
20 1.137(b). Accordingly, the Patent Office refused to revive the '505 application under 37 C.F.R.  
21 1.137(b).

22       **114.** The Patent Office informed the applicants that they might be able to revive the '505  
23 application under the provisions of 37 C.F.R. 1.137(a). However, the Patent Office explained that  
24 "in view of the fact that this case has been abandoned for an inordinate period of time, petitioner  
25 must show diligence between the time of becoming aware of the abandonment of the above-  
26 identified application and the filing of a petition to revive."

27       **115.** The applicants declined to seek relief pursuant to 37 C.F.R. 1.137(a), thereby  
28 acquiescing to the Patent Office's determination that the '505 patent was abandoned on February

1 6, 1993.

2       **116.** Concurrent with their ultimately unsuccessful effort to revive the '505 application,  
3 on May 3, 1994, the applicants filed a new original application that the Patent Office designated as  
4 Serial No. 08/238,080 (the "'080 application"). In the '080 application, the applicants did not  
5 initially disclose to the Patent Office that the application was virtually identical to one that they  
6 intentionally abandoned in the '505 application or of the fact of that abandonment. In addition, the  
7 applicants also failed initially to disclose the fact of their concurrent efforts to revive the '505  
8 application. Furthermore, notwithstanding the fact that the applicants knew and intended that the  
9 '080 application should be treated as a new original application, applicants did not submit new  
10 oaths from the alleged inventors for the '080 application. The applicants also failed to disclose to  
11 the Patent Office that, as an original application, the claims of the '080 application were  
12 anticipated by the prior publication on August 23, 1989, of the applicants' own European  
13 application corresponding to the '920 application, European Application No. 88312135.2 (EP  
14 0328829).

15       **117.** As a result of the applicants' intention to treat the '080 application as an original  
16 application and their concurrent failure to submit new oaths to support that application, on June 3,  
17 1994, the Patent Office issued a notice to the applicants by which the Patent Office indicated that it  
18 had noted that the applicants had failed to file proper oaths or declarations for the '080 application.

19       **118.** In response to the Patent Office's notice to file the missing oaths necessary to  
20 support the '080 application, on July 5, 1994, the applicants submitted a formal response to that  
21 notice by which response the applicants first disclosed the prior abandonment of the '505  
22 application and petitioned the Patent Office to consider the '080 application as a continuation  
23 application to the abandoned '505 application. The applicants' concurrently petitioned the Patent  
24 Office to consider the '080 application as filed under 37 C.F.R. § 1.60 as a continuation of their  
25 previously-abandoned '505 application. However, through this response and the petition  
26 incorporated therein, the applicants continued to misrepresent the prior abandonment of the '505  
27 application and invention as "unintentional."

28       **119.** On October 27, 1994, the Patent Office formally dismissed the applicants' petition



1 to revive the '505 application. As of October 27, 1994, when the petition to revive the '505  
2 applications was denied, the effective filing date for the '080 patent was its own filing date, May 3,  
3 1994.

4 **120.** The applicants did not disclose the decision denying the petition to revive the '505  
5 application to the branch of the Patent Office handling the applicants' petition in the '080  
6 application to treat the '080 application as a continuation application to the '505 application. In  
7 any event, however, on March 14, 1995, the Patent Office formally dismissed that petition as moot  
8 and declared that the '080 application would be processed with a filing date of May 3, 1994.

9 **121.** The Patent Office decisions denying the applicants' petitions to revive the '505  
10 application and to treat the '080 application as a continuation of the '505 created significant,  
11 indeed insurmountable, impediments to the applicants' desire to recant and reverse their earlier  
12 abandonment of the '505 application and the alleged invention comprising the amplification  
13 methods presented therein. Among other problems raised by those decisions, the applicants knew  
14 that unless they could manipulate the priority claim for the '080 application, their own prior  
15 publications would constitute statutory bars to patentability.

16 **5. Applicants' Efforts to Fraudulently Manufacture Claims of Priority for**  
17 **the '080 Application**

18 **122.** In light of the foregoing fatal impediments to patentability of the method claims  
19 presented in the '080 application, the applicants then proceeded to manufacture a scheme to  
20 undermine the Patent Office decisions denying their ability to claim priority for the '080  
21 application back through the '505 application. As the first step in that scheme, on December 5,  
22 1995, the applicants submitted a preliminary amendment in the '080 application in which they  
23 claimed, for the first time, that the '080 application was a divisional application to the '657  
24 application that the applicants filed on March 8, 1995 to pursue the instrument claims and  
25 invention first claimed in the '468 application. This claim of priority resulted from the deliberate  
26 and intentional choice of counsel for the applicants.

27 **123.** The applicants' efforts to change the claim of priority of the '080 application to the  
28 '657 application were improper for several reasons. First, as indicated above, the applicants had

1 previously elected to pursue only instrument-related claims in the '657 application (and earlier  
2 instrument-related applications). Second, the applicants' efforts to claim that the '080 application  
3 was a divisional application of the '657 application was additionally defective because the  
4 specification and claims of the '080 patent are different from and not supported by the  
5 specification and claims of the '657 application. Furthermore, the inventors on the '657  
6 application were not the same as the inventors on the '080 application, and the '657 inventors  
7 could not have effectively disclosed the subject matter of the invention claimed in the '080  
8 application.

9       **124.** However, in addition to the foregoing defects, the effort to claim priority for the  
10 '080 application also violated at least two fundamental requirements necessary to claim priority to  
11 the '657 chain of applications. First, as noted earlier, a claim of priority under Section 120  
12 requires continuity of at least one inventor of common subject matter. (See discussion  
13 hereinabove.) In this case, applicants claimed that the '080 application met that requirement  
14 because Mark Collins was an inventor for the '657 application and also an inventor for the '080  
15 application.

16       **125.** Yet, as noted above, Collins contribution to the '657 application was solely limited  
17 to the concept of target capture and did not include the concept of amplification. As such, the only  
18 subject matter, if any, common to both the '080 application and the '657 application was target  
19 capture. Because all of the claims of the '080 application require both target capture and  
20 amplification, the claims of the '080 application are not entitled to claim priority earlier than the  
21 filing date of the '080 application – May 3, 1994.

22       **126.** Vysis did not disclose the limited contribution of Mark Collins in its claim to  
23 priority through the '657 application and ultimately to the '920 application. The Patent Office  
24 would not have and did not otherwise discover that limited contribution prior to issuance of the  
25 '338 patent. In addition to the validity issues raised thereby, the failure to disclose that  
26 information constituted an independent act of inequitable conduct.

27       **127.** In addition, in applicants' zeal to implement their inequitable scheme to overcome  
28 the Patent Office determination that the claims of the '080 application were only entitled to claim

1 priority as of May 3, 1994, the applicants overlooked a further and equally significant defect in  
2 their effort to claim priority for the '080 application to the '657 application. Under the patent laws  
3 and regulations, an application is only entitled to claim priority to a prior application if such  
4 application was co-pending when the application claiming priority was first filed. Yet, with  
5 respect to the applicants' scheme to advance the priority of the '080 application, their claim to  
6 priority to the '657 application violated this requirement of co-pendency because the applicants did  
7 not file the '657 application until March 8, 1995, nearly one year *after* the applicants filed the '080  
8 application! The applicants failed to advise the Patent Office of this lack of co-pendency in their  
9 December 5, 1995, preliminary amendment. The applicants knew, or should have known, that the  
10 representation that the '080 application was a divisional of the '657 application was improper, and  
11 that the applicants made this representation with the intent of deceiving and misleading the Patent  
12 Office.

13 **6. The Request for Certificate of Correction Filed for the '338 Patent**

14 **128.** The '338 patent issued from the '080 application on May 12, 1998. On December  
15 14, 1998, the applicants submitted a Request for Certificate of Correction for the '338 patent.

16 **129.** Prior to filing the December 14, 1998, Request for Certificate of Correction for the  
17 '338 patent, the applicants identified two fatal defects in the claimed priority for the '338 patent,  
18 the first involving patent application Serial No. 07/648,468 and patent application Serial No.  
19 07/136,920 and the second involving patent application Serial No. 08/238,080 and patent  
20 application Serial No. 08/400,657.

21 **130.** By the December 14, 1998, Request for Certificate of Correction, the applicants  
22 attempted to cure these fatal defects.

23 **131.** First, the applicants sought to change the claim of priority for the '080 application  
24 from a claim that it was a divisional of the '657 application to a claim that it was a continuation of  
25 the '826 application. (The '826 application had been pending when the '080 application was filed,  
26 but had already been abandoned when the Patent Office dismissed the applicants' petition to revive  
27 the '505 application.) This change was sought to avoid invalidity of the '338 patent.

28 **132.** Second, the applicants sought to change the claim of priority made for the '468

1 application from a claim that it was a continuation-in-part of the '920 application to a claim that it  
2 was a continuation-in-part of the '967 application. (The '920 application had already been  
3 abandoned when the '468 application was filed.) This change was sought to avoid invalidity of the  
4 '338 patent.

5 133. By the December 14, 1998, Request for Certificate of Correction the applicants  
6 attempted to cure fatal defects in the '338 patent by, among other things, representing to the Patent  
7 Office that the prior intentional choices made by patent counsel as to which "correction" was  
8 sought were "mistakes" and that those mistakes were of "minor character."

9 134. By the December 14, 1998, Request for Certificate of Correction the applicants  
10 attempted to cure fatal defects in the '338 patent by, among other things, representing to the Patent  
11 Office that the prior intentional choices made by patent counsel as to which "correction" was  
12 sought resulted from errors made in good faith by the applicants. The applicants knew that the true  
13 facts were that neither the request for Certificate of Correction nor any act after the abandonment  
14 of the '505 application was undertaken by applicants in good faith.

15 135. By the December 14, 1998, Request for Certificate of Correction, the applicants  
16 attempted to cure fatal defects in the '338 patent by, among other things, misrepresenting to the  
17 Patent Office the date of applicants' discovery of the mistakes for which correction was sought.  
18 The applicants knew that the true facts were that defects had been discovered earlier than they  
19 disclosed to the Patent Office.

20 136. By the December 14, 1998, Request for Certificate of Correction, the applicants  
21 attempted to cure fatal defects in the '338 patent by, among other things, representing to the Patent  
22 Office that the '505 application had been inadvertently and unintentionally abandoned. The  
23 applicants made this representation knowing that the true facts were that the '505 application was  
24 intentionally abandoned.

25 137. The applicants further represented in the Request for Certificate of Correction for  
26 the '338 patent that the '338 patent was a continuation of the '826 application. However, the '338  
27 patent could not be a continuation of the '826 application, because the disclosure of the '338 patent  
28 was not identical to the disclosure of the '826 application. The applicants knew that the '338

1 patent could not be a continuation of the '826 application. As a direct result of the deceptive  
2 conduct of applicants set forth herein, the certificate of correction was entered by the Patent Office  
3 on September 7, 1999.

4 **7. Applicants' Petition under 37 C.F.R. §1.182**

5 **138.** On December 14, 1998, the applicants filed a petition with the Patent Office under  
6 37 C.F.R. § 1.182 to amend the "specific references" and claims of priority stated in the '826,  
7 '749, and '468 applications so as to attempt to further cure one of the fatal defects in the priority  
8 claim for the '338 patent. At the time of such petition, however, the applicants had previously  
9 intentionally abandoned the '826, '749, and '468 applications and those applications had been  
10 abandoned for more than four years.

11 **139.** The applicants did not petition to revive the abandoned applications prior to seeking  
12 to make amendments. In order to overcome the impediment to its effort to cure the fatal defect in  
13 the claim of priority for the '338 patent arising in the '826, '749, and '468 applications, the  
14 applicants argued in its petition to amend the '826, '749, and '468 applications that an  
15 intentionally abandoned application could be amended after abandonment.

16 **140.** In petitioning to amend the three abandoned applications, applicants did not  
17 disclose to the PTO that they were seeking to circumvent applicants' abandonment of the '505  
18 application nor did they even disclose the existence of that prior application.

19 **141.** As direct result of the deceptive conduct of applicants set forth herein, the petitions  
20 to amend the abandoned applications were granted by the PTO in a decision mailed July 1, 1999.

21 **a. Even if the priority date of the '338 patent is December 21, 1987,**  
22 **isolation of target polynucleotides from a sample by capture on a**  
**solid support is disclosed in the prior art.**

23 **142.** Even assuming the validity of Vysis' claimed December 21, 1987 priority date,  
24 third-party prior art exists that renders the '338 patent invalid under Sections 102 and 103. When  
25 scientists first began to undertake nucleic acid hybridization in the early 1960's, they quickly  
26 recognized that hybridization proceeded more efficiently if the target nucleic acid sequence was  
27 separated from other matter present in a sample or cellular extract. Several techniques were  
28 developed to accomplish such separation, such as density gradient centrifugation. The discovery

1 that single-stranded DNA strongly adhered to some solid supports, such as nitrocellulose  
2 membrane, made it possible to capture DNA on such a support for hybridization. Capture of a  
3 nucleic acid on a solid support, including nitrocellulose membranes, was described in numerous  
4 publications in the 1960's, including Gillespie, D. and Spiegelman, S. "A Quantitative Assay for  
5 DNA-RNA Hybrids with DNA immobilized on a Membrane," *J. Mol. Biol.* 12,829-842 (1965).

6 143. In 1975, E.M. Southern described a method whereby DNA fragments could be first  
7 separated and purified, transferred to a solid support (Southern transfer), and then identified by  
8 hybridization.

9 144. By 1985, scientists had improved capture methods using filters or membranes by  
10 the use of sandwich hybridization methods. In such methods, a nucleic acid sequence  
11 complementary to the target nucleic acid was affixed to a support, the target in solution was  
12 hybridized to the sequence fixed to the support, and a third labeled nucleic acid probe was  
13 hybridized to the target, thus forming the sandwich comprised of the fixed nucleic acid, the target  
14 nucleic acid, and the nucleic acid probe. Dunn, *et al.*, *Cell*, 12:23-36 (1977) (two-step sandwich  
15 hybridization assay); Syvanen *et al.*, *Nucleic Acids Res.* 14, 12:5037-5048 (1986) (one-step  
16 sandwich hybridization assay). These nucleic acid sandwich assays were analogous to earlier  
17 sandwich antibody-antigen assays (immunoassays) in which a solid support containing a bound  
18 capture antibody was used to capture a target antigen from a specimen and then a labeled antibody  
19 was bound to the captured antigen. The labeled antibody was often labeled with an enzyme that  
20 would amplify a signal due to the presence of the labeled antibody by its repeated production of a  
21 detectable product from a substrate for the enzyme in the assay. Both nucleic acid and antibody-  
22 based sandwich assays are assays in which a "ligand" binds to its "ligate."

23 145. The term "capture probe" in connection with hybridization assays refers to a nucleic  
24 acid sequence fixed (or capable of becoming fixed) to a solid support, where that sequence is  
25 complementary to the sequence of the target nucleic acid that is to be captured. Nucleic acid assays  
26 that relied on sandwich hybridization techniques were known before the filing date of the '338  
27 patent as shown by the following references.

28 146. U.S. Patent No. 4,563,419 (Ranki, issued January 7, 1986) discloses a hybridization

1 assay in which target nucleic acid is isolated from a sample by hybridizing it to a complementary  
2 capture probe immobilized on a solid support (nitrocellulose filter) and separated from the sample  
3 by washing. The captured target polynucleotide is detected with a labeled probe.

4       **147.** Scientists also developed sandwich hybridization methods that did not rely on using  
5 nitrocellulose as the solid support. Polsky-Cynkin, *et al.*, *Clin. Chem.* 31/9:1438-1443(1985)  
6 describe DNA hybridization assays in which target DNA is captured by a complementary probe  
7 affixed to a solid support. The solid supports employed included agarose beads (which are  
8 "retrievable" supports, as that term is defined in the '338 patent), polypropylene test tubes and  
9 polypropylene solid-phase receptacles (*e.g.*, see p. 1439). The captured target DNA on the solid  
10 support is separated from the sample and detected with a radiolabeled probe. Beads with  
11 magnetic, paramagnetic, and super paramagnetic properties were also used as retrievable solid  
12 supports, permitting the captured nucleic acid, bound to the support, to be easily removed from the  
13 sample. Advanced Magnetics Inc. (Cambridge, Massachusetts) was an early leader in the  
14 development and sale of such magnetic beads, and obtained patents for these inventions, including  
15 U.S. Patent No. 4,554,088 (Whitehead *et al.*, issued November 19, 1985) and U.S. Patent No.  
16 4,672,040 (Josephson, issued June 9, 1987).

17       **148.** U.S. Patent No. 4,554,088 (Whitehead, issued November 19, 1985) discloses the  
18 use of single-stranded nucleic acid bound to dispersible magnetic beads to isolate complementary  
19 nucleic acid from a sample. The nucleic acid capture probe immobilized on a magnetic bead is  
20 employed as a "ligand" to bind its soluble "ligate", which is the complementary nucleic acid in the  
21 sample (see Table III, col. 17). The magnetic beads bound to target nucleic acid are magnetically  
22 separated from the sample and unbound (non-target) species are removed by washing (col. 17, 11.  
23 36-40).

24       **149.** U.S. Patent No. 4,672,040 (Josephson, issued June 9, 1987) discloses isolating  
25 specific nucleic acid sequences from a sample by contacting capture probes immobilized on  
26 dispersible magnetic beads with a sample containing complementary target polynucleotides and  
27 separating the support and bound polynucleotides from the target. In particular, Josephson states:

28       Specific DNA or RNA fragments can also be isolated from genomic and cloned

1 DNA by immobilization of a known probe to the magnetic particles and placing  
2 the coupled particles in contact with a mixture of nucleic acid fragments,  
3 including the desired species. After hybridization the particles may be  
magnetically separated from unbound materials, washed, and the hybridized  
molecules isolated. (Col. 19, 11.3-10).

4 Josephson further states that the magnetic particles can be used in binding assays (col. 16, 11. 13 *et*  
5 *seq.*).

6 **b. Even if the priority date of the '338 patent is December 21, 1987,**  
7 **amplification of target polynucleotides, or target-like molecules,**  
8 **is disclosed in the prior art.**

9 **150.** As of the filing date, scientists had developed and used a number of molecular  
10 biology techniques to make copies of a target polynucleotide or produce molecules (sometimes  
11 referred to as "reporter" molecules) by virtue of the presence of the target polynucleotide. These  
12 techniques included cloning, cell-free translation, and synthesis of cDNA from mRNA.

13 **151.** The specification of the '338 patent purports to disclose three types of *in vitro*  
14 amplification: non-specific transcription of DNA by *E. coli* RNA polymerase (Example 4);  
15 nonspecific enzymatic amplification of DNA by DNA polymerase primed by random hexamer  
16 primers with and without non-specific transcription (Examples 5 and 6); and non-specific  
17 amplification using Q $\beta$  replicase enzyme (Example 7). To the extent that any of these methods  
18 might be used to replicate a target polynucleotide, they were each disclosed in the art prior to  
19 December 21, 1987. All of these methods would result in formation of a random and  
heterogeneous collection of fragments of any portion of the starting population of polynucleotides.

20 **152.** The use of *E. coli* RNA polymerase core enzyme to transcribe DNA into RNA *in*  
21 *vitro* was well known in the prior art, as acknowledged by the patentees in their citation in  
22 Example 4 to R. Burgess in *RNA Polymerase*, Cold Spring Harbor Press, pp. 69-100 (1976) ('338  
23 patent, col. 30, 11. 62-64). In the absence of sigma protein, *E. coli* RNA polymerase initiates  
24 synthesis at any position in a DNA molecule. The use of random hexamer oligonucleotide primers  
25 to initiate non-specific enzymatic reproduction of polynucleotides was also known in the art, for  
26 example, as disclosed in Feinberg *et al.*, *Anal. Biochem.* 132:6-13 (1983). It was well-known in the  
27 art that DNA polymerases required primers to initiate replication. To the extent that RNA  
28 sequences can be transcribed under certain conditions using the enzyme Q $\beta$  replicase, patentees



1 have acknowledged that this is also known in the art by their citation of Blumenthal, *Proc. Natl.*  
2 *Acad. Sci. U.S.A.* 77:2601-2605 (1980) (at col. 32, 11. 16-17).

3       **153.** Besides the amplification methods described in the '338 Patent, other methods of  
4 making additional copies of a polynucleotide, or of a reporter molecule, were well known in the art  
5 before the filing date. For example, Gaubatz *et al.*, *Biochim. Biophys. Acta* 825:175-187 (1985)  
6 had described a method of amplifying cDNA sequences by a DNA polymerase-mediated strand  
7 displacement synthesis.

8       **154.** Signal or probe amplification methods were developed in which the detection probe  
9 was labeled with enzymes that could amplify the signal generated when the detector probe bound  
10 to the target. For example, Kourilsky, *et al.*, (U.S. Patent No. 4,581,333, April 8, 1986) disclose  
11 the use of enzyme-labeled probes for use in diagnostic assays. The Kourilsky patent incorporates  
12 by reference the disclosures of Manning, *et al.*, *Biochemistry* 16:1364 (1977) as a hybridization  
13 technique in which the enzyme-labeled probes may be employed. Manning, *et al.* employed target  
14 capture techniques to isolate rRNA genes.

15       **155.** Other signal amplification methods used the enzyme Q $\beta$  replicase to make  
16 additional copies of the label affixed to the detector probe that had hybridized to the target. Such  
17 techniques were disclosed in Chu *et al.*, *Nucleic Acids Research* 14(14):5591-5603 (1986) and the  
18 corresponding United States patent, which was filed before December 21, 1987 (U.S. Patent No.  
19 4,957,858 (Chu *et al.*, September 18, 1990).

20       **156.** Moreover, the polymerase chain reaction ("PCR") method of target amplification  
21 using specific primers had been described in a number of publications before December 21, 1987  
22 (e.g., Mullis *et al.*, *Cold Spring Harb. Symp. Quant. Biol.* LI:263-273 (1986); Saiki *et al.*, *Nature*  
23 324:163-166 (1986); Wong *et al.*, *Nature* 330:384-386 (1987). Applications for United States  
24 patents for the PCR method were also filed before then, including U.S. Patent No. 4,683,202  
25 (Mullis). The PCR method involves the use of specific primers to identify unique nucleic acid  
26 sequences of the target organism to be copied *in vitro* by a DNA polymerase. Thus, as of  
27 December 21, 1987, methods of amplifying a target polynucleotide, or a reporter molecule based  
28 on the presence of the target polynucleotide, were well known to those skilled in the art.

1 c. Even if the priority date of the '338 patent is December 21, 1987,  
2 the combination of target capture on a solid support with  
3 amplification of the isolated polynucleotide is disclosed in the  
4 prior art, as is the motivation to combine target capture with  
5 amplification.

6 157. Following the discovery of reverse transcriptase in 1970, the development of DNA  
7 cloning in 1973, and DNA sequencing in 1975, methods were developed for detecting normal and  
8 mutant genes and for detecting and identifying infectious organisms in clinical samples. Almost  
9 all techniques used to study nucleic acids require that the nucleic acids be treated to remove or  
10 inactivate cellular components that rapidly degrade nucleic acids or that otherwise interfere with  
11 further manipulations. In addition, the low frequency of individual genes in the genome and/or the  
12 low concentration of individual gene expression products in soluble cellular components also  
13 require isolation and concentration of these nucleic acids from biological materials prior to further  
14 study. Therefore, scientists were motivated to develop methods to separate and/or concentrate  
15 individual genes from other cellular components, some of which could inhibit amplification or  
16 detection reactions. Many such procedures were known in the art prior to 1987, and it was easy  
17 and commonplace for scientists to combine various methods to isolate and concentrate particular  
18 nucleic acids from various biological materials. By combining multiple methods, scientists could  
19 obtain greater degrees of purity and concentration than could be achieved by a single method  
20 alone. In addition, scientists were motivated to produce copies of, or amplify, individual gene  
21 sequences to provide sufficient quantities for analysis and detection. Recombinant DNA cloning  
22 was one method that allowed scientists to isolate discrete DNA fragments from any organism and  
23 produce large amounts of the same DNA for further characterization. Although the desired nucleic  
24 acid can easily be made in abundance once it has been cloned, the initial DNA cloning itself is a  
25 laborious process. For example, starting from genomic DNA or DNA transcribed from  
26 unfractionated messenger RNA, a scientist usually had to screen many clones before finding one  
27 that contained the desired genetic sequence. See, e.g., Maniatis *et al.*, *Molecular Cloning A*  
28 *Laboratory Manual* (Cold Spring Harbor Laboratory, Cold Spring Harbor, NY 1982), pp. 309-362.

158. To increase the frequency of clones with a desired target sequence, scientists often  
isolated mRNA from tissue that specifically produced the target gene product because the absolute

1 and relative amounts of the desired target mRNA are greater. For example, mRNA was isolated  
2 from pancreatic islet cells to enrich for sequences encoding insulin. Methods were developed to  
3 separate mRNA from DNA, other RNAs, and to enrich the desired target and to remove cellular  
4 components that might interfere with the cloning process. Among the most commonly used  
5 methods was chromatography in which the poly(A) tail of mRNA hybridized to a complementary  
6 oligo(dT) on a solid support, i.e., target capture (see Maniatis *et al.*, *supra*, Chapter 6). The  
7 isolated mRNA could then be converted to cDNA using reverse transcriptase, and the DNA was  
8 cloned and amplified by replication in bacterial cells. Thus, before the filing date, scientists  
9 routinely employed the combination of target capture and amplification to generate detectable  
10 amounts of nucleic acid sequences of interest.

11       159. Due, in part, to the laborious nature of amplification by cloning, scientists  
12 developed methods for *in vitro* amplification of nucleic acid sequences of interest, including those  
13 discussed above. Since scientists were aware that substances present in samples, *e.g.* polymerase  
14 inhibitors, could interfere with these methods of amplification, they were motivated to employ  
15 known target capture methods to purify the samples prior to *in vitro* amplification just as they had  
16 done for cloning, a process that includes steps carried out both *in vitro* and *in vivo* that may be  
17 adversely affected by impurities in the target nucleic acids.

18       160. Molecular biology techniques have been applied to the diagnosis of disease for  
19 decades. The sandwich assays discussed above, including both nucleic acid hybridization assays  
20 and immunoassays, have been used to detect infectious agents. Many sandwich assays employ a  
21 combination of target capture and amplification to enhance detection sensitivity. A representative  
22 sandwich assay of this type is disclosed, for example in U.S. Patent No. 4,925,785, which was  
23 filed on March 7, 1986 and issued on May 15, 1990. This reference describes an assay that  
24 employs capture of a target on a solid support and amplification of signal generation by using  
25 secondary probes.

26       161. Sandwich assays were used to capture the target upon a solid support prior to  
27 December 21, 1987 because scientists recognized that the presence of additional matter in the  
28 sample could interfere with the sensitivity of the assay (*e.g.*, by interfering with an enzyme used to

1 generate the amplified signal). Capture on a solid support was recognized as a means for reducing  
2 the inhibitory effects of these other components commonly found in a sample.

3       **162.** In some clinical samples, the number of infectious organisms present in the sample  
4 is small. To detect small numbers of target, the test sensitivity must be high. Diagnostic tests based  
5 solely on hybridization between complementary DNA sequences often lack sensitivity when the  
6 number of infectious agents in the sample is small because the signal over background that can be  
7 generated from a low number of hybrids is insufficient for reliable detection. Thus, scientists used  
8 amplification to enhance the signal obtained from the probe-target hybrids. For example, the  
9 probes were labeled with enzymes that would repeatedly transform a substrate into product to  
10 amplify the signal and enhance the sensitivity of detection. Alternatively, the microorganisms in  
11 the sample could be grown in culture before the hybridization assay was performed to increase the  
12 number of target organisms, and hence amplify the target sequences present in the sample tested.

13       **163.** Prior to December 21, 1987, one skilled in the art would have been motivated to  
14 combine technologies, such as nucleic acid hybridization, target capture, and amplification  
15 methods, to obtain the desired specificity and sensitivity in an assay that detects sequences of  
16 interest. An abundance of evidence indicates that the idea of capturing nucleic acids onto a solid  
17 support and enhancing detection of those nucleic acids by an amplification process was widely  
18 known by those skilled in the art prior to that date.

19       **164.** For example, prior to the filing date it was well known among those skilled in the  
20 art that a polynucleotide of interest could be purified from a sample by contacting it with a solid  
21 support that would bind the polynucleotide and then separating the bound target from the sample.  
22 Purification would remove components in the sample that would otherwise prevent or inhibit  
23 further manipulation (e.g., cloning or *in vitro* amplification) of the target polynucleotide.

24       **165.** One method commonly used to purify mRNA before the filing date involves  
25 contacting poly(A)-tailed mRNA in a biological sample with oligo(dT) bound to a solid support  
26 (e.g., cellulose) under conditions that permitted hybridization of the poly(A) tail with the oligo(dT)  
27 moiety (see Maniatis *et al.*, *supra*, Chapter 6). After separating the support and bound mRNA from  
28 the sample, the purified mRNA could then be released from the solid support and used in a variety

1 of ways (e.g., in cDNA synthesis and/or molecular cloning). For example, Gaubatz *et al.*, *Biochem.*  
2 *Biophys. Acta* 825:175-187 (1985) described the isolation of poly(A)+ mRNA using oligo(dT)-  
3 cellulose chromatography followed by conversion of the purified mRNA into cDNA and further  
4 amplification using the Klenow fragment of DNA polymerase.

5       **166.** Sequence-specific capture of a target polynucleotide was also well known in the art  
6 before December 1987. This could be accomplished by contacting a sample containing the target  
7 polynucleotide with a solid support and a capture probe that was capable of binding the solid  
8 support and that contained a sequence of nucleotides complementary to the target polynucleotide.  
9 For example, U.S. Patent No. 4,672,040 (Josephson) and U.S. Patent No. 4,554,088 (Whitehead, *et*  
10 *al.*) describe use of dispersible solid supports (magnetic beads) with bound polynucleotide capture  
11 probes for isolating target polynucleotides. By separating the magnetic beads with their adherent  
12 target polynucleotide, the target polynucleotide is separated from other sample components  
13 capable of inhibiting or negatively affecting further manipulation (e.g., detection) of the target  
14 polynucleotide.

15       **167.** Prior to the filing date of the '338 patent, the scientific literature had also taught that  
16 it would be useful to combine the techniques of target capture and amplification to enrich and  
17 detect target polynucleotides. For example, U.S. Patent No. 4,957,858 (Chu *et al.*) teaches an assay  
18 in which a reporter polynucleotide is amplified using the enzyme Q $\beta$  replicase. The patent states  
19 that the assay method can be carried out on a raw specimen of biological material, but more  
20 typically is carried out on a sample processed "to remove materials that would interfere with  
21 detection" (see col. 7, 11.7-15). The patent further describes a variety of known purification  
22 methods that can be used to isolate the target for the assay, including methods in which nucleic  
23 acid is "isolated from virioids, viruses or cells of a specimen and deposited on solid supports. . ."  
24 (see col. 7, 11. 18-54, particularly 11. 24-28).

25       **168.** Solid supports were widely used to isolate nucleic acids to study their structure and  
26 function or to detect the presence of a particular nucleic acid in a sample. Because the amount of a  
27 target polynucleotide in a sample is often very small, the desirability of increasing the proportional  
28 amount of isolated polynucleotide before further analysis or detection was obvious to one skilled

1 in the art. It was common practice in the art to capture small amounts of mRNA on solid supports,  
2 convert the mRNA to cDNA using reverse transcriptase, an RNA-dependent DNA polymerase,  
3 and then further amplify the cDNA by cloning prior to detecting and/or analyzing the DNA. Once  
4 methods of *in vitro* amplification became widely available, it was obvious to combine these  
5 techniques with target capture on solid supports. Moreover, because target capture was known to  
6 be less than 100% efficient, it would have been obvious to one skilled in the art to combine target  
7 capture with amplification procedures to increase the amount of captured target (i.e., to  
8 compensate for any losses during the capture step) before detection, particularly if the number of  
9 target molecules was, or might be, small.

10       **169.** The motivation of those skilled in the art to proceed in this manner was obvious in  
11 view of the benefit to be obtained. For example, the evidence will show that as of October 1986,  
12 Gen-Probe recognized the benefits of purifying a target for purposes of developing an effective  
13 assay.

14       **170.** This motivation was also described elsewhere. For example, in Brown *et al.*,  
15 "Methods of Gene Isolation" *Ann. Rev. Biochem.*, 43:667-693 (1974), the authors recognized the  
16 desirability of combining target capture on solid supports with amplification. The authors reviewed  
17 a number of methods for isolating nucleic acids of interest, and devoted one section to the use of  
18 polynucleotides fixed to insoluble matrices to isolate DNA. At pages 673-674, they describe using  
19 RNA or DNA fixed to an insoluble support to effect sequence-specific isolation of target DNA  
20 containing a sequence complementary to the probe. In their "Concluding Remarks" (page 687),  
21 Brown *et al.* state that purification of DNA (e.g., using polynucleotides fixed to insoluble matrices)  
22 could be coupled with a method by which, "... a small amount of a given gene can be increased  
23 enormously in amount" such as by an "amplification step. . . carried out *in vitro* by an efficient  
24 DNA polymerase, which would replicate faithfully each molecule of DNA many times."

25       **171.** Arsenyan *et al.*, *Gene* 11:97-108 (1980) also recognized the desirability of  
26 combining target capture with amplification. They described a method to produce "amplified  
27 homogeneous DNA sequences" for the purpose of studying gene arrangement. Their process  
28 captured complementary single strands of the 5S RNA gene by hybridization to probes affixed to

1 cellulose supports followed by elution of the captured strands, annealing of the strands to produce  
2 double stranded DNA which was inserted into a cloning vector, transformation of host cells with  
3 the vector, and amplification of the DNA by growing the transformed host cells. As of the filing  
4 date of the '338 Patent, it would have been obvious to one of ordinary skill in the art that other  
5 known amplification methods including those described above could have been substituted for the  
6 cloning method used by Arsenyan *et al.* The obviousness of such substitution is suggested by the  
7 patentees' broad definition of "amplify" in the '338 Patent (col. 2, lines 9-19). Substituting other  
8 methods of amplification for amplification by cloning would have been obvious to one skilled in  
9 the art by December 1987.

10 172. For example, Gaubatz *et al.*, *Biochem. Biophys. Acta* 825:175-187 (1985) described  
11 the isolation of mRNA by using oligo(dT)-cellulose chromatography followed by conversion of  
12 the purified mRNA into cDNA and amplification of the cDNA using polymerase-mediated strand  
13 displacement procedure. Powell *et al.*, *Cell* 50:831-840 (1987) described isolating poly(A) + RNA  
14 by oligo(dT)-cellulose chromatography to capture mRNAs of interest, followed by synthesis of  
15 cDNA and PCR amplification of the cDNA and detection of specific sequences of interest.

16 173. Two additional references show that purification of a target nucleic acid on a solid  
17 support (i.e., chromatography) and amplification of the target *in vitro* by using the enzyme Q $\beta$   
18 replicase was known before the filing date: Feix *et al.* "Replication of Viral RNA, XVI.  
19 Enzymatic synthesis of infectious viral RNA with noninfectious Q $\beta$  minus strands as template,"  
20 *Proc. Natl. Acad. Sci. USA* 59 (1): 145-152 (1968), and Pollet *et al.*, 1967, "Replication of Viral  
21 RNA, XV. Purification and properties of Q $\beta$  minus strands," *Proc. Natl. Acad. Sci. USA* 58 (2):  
22 766- 773 (1967). Feix *et al.*, 1968, disclose (1) purification of a target RNA species (minus  
23 strands of bacteriophage Q $\beta$  RNA) in a series of steps that includes binding the target RNA to a  
24 support and separating the desired RNA species bound to the support from other sample  
25 components (i.e., cellulose chromatography), and (2) *in vitro*, exponential synthesis of more RNA  
26 from the isolated target RNA strands to amplify the amount of desired RNA. The *in vitro*  
27 synthesis reaction used Q $\beta$  replicase to produce about three times the input RNA after four  
28 minutes, which was detected as incorporation of radioactive nucleotides and as the generation of

1 infectious RNA measured in an *in vitro* transfection assay.

2       174. The purification procedure disclosed by Feix *et al.* is described in more detail by  
3 Pollet *et al.*, (1967) who disclosed a multi-step method of purifying bacteriophage Q $\beta$  minus  
4 strands from double-stranded viral RNA (dsRNA) comprising minus and plus strands. In  
5 particular, this method includes the steps of contacting a viral RNA sample with a solid support  
6 (cellulose) that separates dsRNA from single-stranded RNA (ssRNA), to ultimately produce a  
7 purified ssRNA that was predominantly minus strands.

8       175. The Feix *et al.* reference alone provides all of the method steps recited in claim 1 of  
9 the '338 patent because it describes the purification procedure of Pollet *et al.* and a method for  
10 amplifying the isolated target polynucleotide *in vitro* to produce more RNA which was detected by  
11 both physical and biological methods. Together, the Feix *et al.* and Pollet *et al.* references provide  
12 all of the information one skilled in the art would need to make the inventions claimed in the '338  
13 patent obvious.

14       176. As discussed above, U.S. Patent No. 4,957,858 (Chu *et al.*) disclosed a method of  
15 replicating a reporter nucleic acid using an enzyme called Q $\beta$  replicase, typically on a processed  
16 specimen derived from a raw specimen to remove materials that would otherwise interfere with  
17 detection. As disclosed in materials related to the '858 patent, as of March 1985 certain of the  
18 inventors of the technology claimed in the patent had conceived of a technique for using Q $\beta$   
19 replicase for signal amplification that involved capture of the target DNA or RNA upon a solid  
20 support such as nitrocellulose or nylon membrane. In an Invention Report and Record dated  
21 February 8, 1985, submitted to the Department of Health and Human Services on March 27, 1985,  
22 Drs. Lizardi, Kramer and Mills described a technique of nucleic acid hybridization in which a  
23 sample containing DNA or RNA "is immobilized on a solid support" and subsequently detected  
24 with a recombinant RNA molecule that is "replicated faithfully to generate millions of copies" by  
25 using Q $\beta$  replicase (Disclosure of Invention, pages 1-4). Other materials related to the '858 patent  
26 show that as of December 1987, certain of the inventors of the technology claimed in the patent  
27 had conceived of a technique for using Q $\beta$  replicase for signal amplification that involved capture  
28 of the target DNA or RNA upon solid supports in accordance with known sandwich hybridization



1 techniques. See Manuscript by, Lizardi *et al.*, "Billion-fold amplification of recombinant-RNA  
2 hybridization probes," submitted for publication 12/18/81 (VI 104595-VI 104618), particularly  
3 page 12 (VI 104606), first full paragraph and reference cited therein. A related U.S. Patent, U.S.  
4 Patent No. 5,989,817 (Soderlund, *et al.*, issued November 23, 1999), filed before the filing date of  
5 the '338 patent, discloses assay methods for nucleic acids employing hybridization techniques  
6 where, following a capture step, detector probes are incorporated into target nucleic acids and  
7 amplified.

8 177. Vysis never achieved any commercial success with the inventions claimed in the '338  
9 patent. Vysis never developed any product with such methods, never achieved FDA approval of  
10 such a product, and never obtained any revenue from such a product.

11 178. Gen-Probe contends that no evidence concerning Gen-Probe's conduct with respect  
12 to, or products incorporating, TMA methods will provide relevant evidence in this case as to  
13 secondary considerations of non-obviousness, which must be determined with respect to the  
14 claimed invention (e.g., an invention incorporating non-specific amplification).

15 179. If evidence of Gen-Probe's conduct and products is determined for any reason to  
16 be relevant in this case, Gen-Probe will demonstrate that the evidence relied on by Vysis is  
17 insufficient to overcome the weight of the prior art as to obviousness and secondary considerations  
18 concerning Vysis' own conduct. If evidence of Gen-Probe's conduct and products is determined  
19 for any reason to be relevant in this case, Gen-Probe will demonstrate a lack of nexus between its  
20 anticipated commercial success and the technology disclosed in the '338 patent. If evidence of  
21 Gen-Probe's conduct and products is determined for any reason to be relevant in this case, Gen-  
22 Probe will demonstrate that it did not "copy" any Vysis technology. Gen-Probe will further  
23 demonstrate that its so-called "collaboration" with Vysis resulted solely from Vysis' offers to  
24 explore settlement of certain prior litigation known as *Regents v. Kohne* and *Center for Neurologic*  
25 *Study v. Kohne*. Gen-Probe will further show that it obtained a license to the '338 patent only after  
26 Vysis took the position that the patent was valid and infringed by Gen-Probe's blood screening  
27 assay, and that the license was acquired in view of Vysis' demonstrated willingness and capability  
28 to commence and maintain meritless litigation, as shown by the *Regents v. Kohne* and *Center for*

1 *Neurologic Study v. Kohne* cases.

2       **180.** The invention claimed in the '338 patent was publicly disclosed not later than August  
3 23, 1989, when Vysis' application for European Patent publication no. 0 328 829 A2 was published.  
4 The European patent '829 application was a copy of the same application that directly led to issuance  
5 of the '338 patent. As a copy of the U.S. application, the European application necessarily disclosed  
6 the invention claimed in the '338 patent.

7       **F. THE '338 PATENT IS UNENFORCEABLE**

8       **181.** Applicants for patents have a general duty of candor and good faith in their dealings  
9 with the Patent and Trademark Office (the "Patent Office") and an affirmative obligation to  
10 disclose to the Patent Office all information that they know to be material to the examination of a  
11 pending application pursuant to 37 C.F.R. § 1.56. This duty extends to the applicants and their  
12 representatives, such as their attorneys, and all others associated with the prosecution, including  
13 every person who is substantively involved in the preparation or prosecution of the application.

14       **182.** The applicants knowingly and willfully concealed and misrepresented material  
15 evidence during the prosecution of the '338 patent applications and that by such inequitable  
16 conduct, the '338 patent is unenforceable against Gen-Probe for the reasons that follow.

17       **1. Applicants' Failure to Disclose all Material Art Known to Them During**  
18       **the Prosecution of the '338 Patent and Misrepresentations as to the**  
19       **State of the Art.**

20       **183.** Despite their intentional failure to disclose the fatal defect in their claim of priority  
21 in the '080 application, the applicants continued to prosecute the claims of that application.

22       **184.** During the course of its prosecution of the claims that ultimately issued in the '338  
23 patent, the applicants concurrently presented counterpart patent applications and patent claims to  
24 international and foreign patent offices. During the course of the examination and prosecution of  
25 those counterpart applications and patent claims, the European Patent Office, for one, identified  
26 and disclosed to the applicants prior art material to the prosecution of the '338 patent claims that  
27 was not before or considered by the United States Patent and Trademark Office in the examination  
28 of the '338 patent. For example, among this prior art of record in the European Patent Office  
proceedings but not in the United States Patent Office was the following: EP-A-0200362 (Cetus

1 Corp.); EP-A-0265244 (Amoco Corp.); EP-A-0154505 (Ortho Diagnostic Systems, Inc.); WO-A-  
2 8605815 (Genetics Int'l Inc.); and WO-A-8701730 (Yale Univ.).

3       **185.** Moreover, further material information known to the applicants was not disclosed  
4 to the Patent Office. For example, in a trip report dated July 22, 1987, inventor Jonathon Lawrie  
5 detailed a visit that he made to the Second Annual ASM Conference on Biotechnology during June  
6 25-28, 1987. The trip report discusses a presentation made by T. Gingeras of SIBIA concerning  
7 assays combining the procedures of target capture and amplification. The trip report also notes  
8 that a similar presentation was made by T. Gingeras the previous year, 1986, which Dr. Lawrie  
9 attended. The fact that Dr. Lawrie attended T. Gingeras' presentation concerning assays  
10 combining target capture with amplification constitutes information that is material to the  
11 patentability of the '338 patent and should have been disclosed to the Patent Office. Nothing in  
12 the file history of the '338 patent indicates that T. Gingeras' work was ever disclosed to the Patent  
13 Office by the applicants.

14       **186.** Additional references known to applicants to be material to the examination of  
15 patent applications for the invention of the '338 patent were not disclosed by applicants to the  
16 Patent Office. These references included U.S. Patent No. 4,957,858 (Chu *et al.*, September 18,  
17 1990) and Manuscript by Lizardi *et al.*, "Billion-fold amplification of recombinant-RNA  
18 hybridization probes," submitted for publication 12/18/81 (VI 104595-VI 104618), particularly  
19 page 12 (VI 104606), first full paragraph and reference cited therein. This manuscript was in the  
20 possession of inventor Jonathon Lawrie in December, 1987

21       **187.** Notwithstanding the applicants' duty to disclose all material information to the  
22 Patent Office, the applicants failed to disclose the foregoing prior art to the Patent Office. In  
23 addition, upon filing the application which led to the issuance of the '338 patent, the applicants did  
24 not submit a Form 1449, citing all known material art to the Patent Office, as required to ensure  
25 that all known material art is considered by the Patent Office. The applicants knowingly and  
26 intentionally failed to submit a Form 1449 and concurrently failed to apprise the Patent Office of  
27 prior art identified in the European Patent Office proceedings and in prior proceedings on related  
28 United States patent applications, in order to deceive the Patent Office and prevent it from

1 considering all relevant prior art. For example, once the '080 application was filed and applicants  
2 thereby incurred a duty to disclose additional references post-dating December 21, 1987,  
3 applicants were required to inform the Patent Office of the public disclosure on August 23, 1989 of  
4 applicants' application for European Patent publication no. 0 328 829 A2 and the publication of  
5 articles in the United States by the inventors describing the invention. The European patent '829  
6 application was a copy of the same application that directly led to issuance of the '338 patent. As a  
7 copy of the U.S. application, the European application disclosed the invention claimed in the '338  
8 patent and was material.

9       **188.** During prosecution of the application that lead to the issuance of the '338 patent, it  
10 was the examiner's position that modification of the known technique of amplification (by  
11 purifying a target nucleic acid from a mixture of nucleic acids using a solid support) was  
12 recognized as offering an advantage that would render this improvement an obvious one. Collins  
13 et al. took the opposite position that the "evidentiary record of the prior art did not teach purifying  
14 target nucleic acids prior to amplification."

15       **189.** During prosecution of the '080 application, the applicants submitted a declaration  
16 of David H. Persing, M.D., Ph.D. Paragraph 12 of that declaration states:

17               Since the addition of such isolation steps would be costly and  
18 time consuming, would further complicate the assay and was  
19 generally believed to be unnecessary; those who are adding  
20 amplification to their nucleic acid hybridization assays had a strong  
21 incentive to avoid the addition of target isolation steps to their  
22 hybridization assays. It was not until much later that it became  
23 apparent that non-specific amplification was occurring despite the  
24 careful selection of primer, i.e., that even careful selection of primers  
25 would not permit the selective amplification of a particular nucleic  
26 acid. I believe this realization did not occur until after December  
27 1987.

28       **190.** Subsequent to the Persing Declaration, the examiner allowed the claims of the  
application. The examiner's reasons for allowance stated "the art at the time of filing did not  
recognize that the efficiency of PCR amplification would decrease due to the presence of  
contaminants in the sample and therefore provided no motivation to purify a target sample from a  
heterogeneous sample of nucleic acid prior to amplification. Having not recognized the problem,

1 applicants' solution therefore, while utilizing routine methodology to modify PCR amplification  
2 techniques, would not have been obvious at the time that the invention was made. The Declaration  
3 of Dr. David Persing, further supports this conclusion...." (Statement of Reasons for Allowance  
4 mailed October 16, 1997).

5       **191.** It is evident from the above that throughout prosecution, inventors Collins et al., by  
6 means of attorney argument and the declaration of Dr. Persing, affirmatively asserted that as of the  
7 December 21, 1987 filing date, those skilled in the art would not have considered isolation of  
8 target nucleic acids before applying amplification techniques. This affirmative assertion is what  
9 persuaded the examiner to allow the claims.

10       **192.** The applicants knew that this assertion was not true. As set forth above concerning  
11 the issues of obviousness and anticipation based on the prior art available as of December 21,  
12 1987, the combination of target isolation (capture) on a solid support with amplification of the  
13 isolated polynucleotide is disclosed in the prior art, and the motivation to combine target capture  
14 with amplification is also in the prior art.

15       **193.** Moreover, the Chu '858 patent teaches an assay in which a reporter polynucleotide  
16 is amplified using the enzyme Q $\beta$  replicase. The Chu patent teaches that the assay method is  
17 carried out on a sample which has been processed "to remove materials that would interfere with  
18 detection" (see Chu '858, col. 7, ll. 7-15).

19       **194.** As of August 27, 1987, prior to the filing date of the '338 patent, Vysis and/or its  
20 predecessor Gene-Trak were well aware that others in the art had developed nucleic acid  
21 amplification strategies. One such strategy was a Q $\beta$  replicase method for which a patent had been  
22 applied for. That application matured as the Chu '858 patent. Because the Chu '858 patent  
23 disclosed that others were aware of the improved results that could be obtained by separation of  
24 the nucleic acid target from the sample before amplification, by withholding the '858 patent from  
25 the examiner the applicants affirmatively misled the examiner during prosecution with regard to  
26 the state of the art as of the December 21, 1987 filing date of the Collins '338 patent.

27       **195.** The applicants were also aware of other material which taught the concept of  
28 polynucleotide separation from a sample and the application of Q $\beta$  replicase amplification. For

1 example, a report submitted for publication in the name of Paul M. Lizardi et al. was provided to  
2 the applicants at least by December 22, 1987, its received date. The article had been submitted for  
3 publication on December 18, 1987. That article states, "in practice, the sensitivity of the assays  
4 will be determined by the efficiency of the method used to remove non-specifically bound probes.  
5 There are a number of promising methods for reducing this background, including 'sandwich  
6 hybridization' techniques. By combining an effective background reduction technique with the  
7 enormous amplification that is inherent in the use of recombinant probes, it should be possible to  
8 develop assays that are able to detect even a small infectious agent in a clinical sample." (Page  
9 12.) By not providing this information to the examiner, the applicants were able to mislead the  
10 examiner regarding the true state of the art surrounding the combination of isolation and  
11 amplification.

12 196. The evidence also demonstrates that certain Q $\beta$  replicase related patent  
13 applications, including that which matured into the Chu '858 patent, were of such potential  
14 commercial significance that Vysis' predecessor, Gene-Trak systems, obtained a license to  
15 operate within the confines of the Chu '858 patent.

16 197. The applicants were obligated to disclose the Chu '858 patent to the attention of the  
17 examiner during prosecution of the Collins '338 patent for several reasons:

18 (a) First, the original claims of the Collins '338 patent did not differentiate  
19 between amplification of the probe and amplification of the target. Original Claim 1 merely  
20 required contacting the sample potentially containing the target with a first support capable of  
21 specifically associating with the target under binding conditions, separating the support from the  
22 remaining sample to form a "removal product" and subjecting the "removal product" to  
23 amplification. The claim does not specifically state that the target is amplified; indeed, the  
24 definition of "amplify" set forth at column 2 of the patent broadly encompasses amplification of  
25 any molecule whose presence indicates the presence of the target. Accordingly, the Chu '858  
26 patent anticipated the original claims of the Collins application. Hence, the Chu '858 patent would  
27 have been highly material prior art;

28 (b) Second, the Chu '858 patent has a typographical error with regard to the

1 filing date of the application which matured into the '858 patent. The face of the patent indicates  
2 the filing date is April 16, 1988. This is a typographical error; the filing date is actually April 16,  
3 1986 (as subsequently established by a Certificate of Correction). The correct filing date was  
4 known to the applicants in that it was referred to in licensing documents. Because the Chu patent  
5 contains an error with regard to the filing date, the examiner would not have considered and cited  
6 the Chu patent as being representative of the prior art because on its face its filing date was  
7 subsequent to the filing date of the Collins '338 patent. Hence, the examiner would have  
8 considered the Chu '858 patent unavailable. The Chu '858 patent should have been brought to the  
9 examiner's attention under these circumstances.

10 (c) Third, because those prosecuting the Collins application had advised the  
11 examiner that those skilled in the art at the time the invention was made would not have isolated  
12 the probe/target complex prior to amplification, they were obligated to advise the examiner  
13 regarding the Chu '858 patent and its applicability to the claims of the Collins application because  
14 it refutes an assertion made during prosecution. See 37 C.F.R. §1.56(b)(2)(ii).

## 15 2. Applicants' Misrepresentations About The Scope of the '080 16 Application

17 198. During prosecution of the application that lead to the issuance of the '338 patent, it  
18 was the examiner's position that modification of a known technique of amplification (by purifying  
19 a target nucleic acid from a mixture of nucleic acids using a solid support) was recognized as  
20 offering an advantage that would render this improvement an obvious one. Collins et al. took the  
21 opposite position that the "evidentiary record of the prior art did not teach purifying target nucleic  
22 acids prior to amplification."

23 199. During prosecution of the '080 application, the applicants submitted a preliminary  
24 amendment on December 5, 1995. This amendment was submitted almost eight years after  
25 applicants filed the first application claiming similar subject matter. In the December 5, 1995  
26 amendment, applicants for the first time suggested that the subject matter represented an  
27 improvement to PCR amplification methods, although applicant's knew that the '080 application  
28 did not encompass specific amplification methods such as PCR and knew that they had not once

1 suggested otherwise during the eight years in which they had prosecuted various related  
2 applications.

3       **200.** During prosecution of the '080 application, the applicants submitted a declaration  
4 of David H. Persing, M.D., Ph.D. on July 9, 1997. The Persing declaration was entirely focused  
5 on PCR amplification. The Persing declaration sought to overcome an obviousness rejection by  
6 contending that those skilled in the art did not recognize until after December 1987 that non-  
7 specific amplification occurred during PCR amplification despite the careful selection of primers.

8       **201.** By this course of conduct, applicants sought to misrepresent the nature of their  
9 invention and claim that invention as an improvement to PCR. Applicants knew these  
10 representations were false and made them with the intent to deceive the Patent Office. Applicants'  
11 course of conduct, including the Persing declaration, successfully misled the Examiner into  
12 believing that the '338 patent encompassed specific amplification. In the Examiner's October 13,  
13 1997 statement of reasons for allowance of the patent, the Examiner stated: "The claims are drawn  
14 to methods of PCR amplification..."

15       **3. Applicants' Misrepresentations About Mullis, U.S. Patent No. 4,683,202**

16       **202.** During the course of that continued prosecution of the '080 application, the Patent  
17 Office rejected applicants' proposed claims to a method of nucleic acid amplification on the  
18 grounds of the disclosure of prior art that included the Mullis patent (U.S. Patent 4,683,202). In  
19 response, the applicants argued that the prior art did not teach or disclose purification of a target  
20 nucleic acid prior to amplification, yet, that argument was false. Specifically, in their December 5,  
21 1995 Preliminary Amendment, the applicants made the following statements regarding the Mullis  
22 patent:

23               Applicants submit the Examiner's conclusion is the product of an  
24 improper picking and choosing of selective disclosure from the  
25 cited references to obtain Applicants' invention and that when the  
26 references are considered for all that they teach the references do  
27 not disclose or suggest Applicants' invention. For example, while  
28 it is true that Mullis (U.S. No. 4,683,202) discloses DNA  
amplification and some improved sensitivity and ability to isolate  
specific nucleoside sequences, Mullis also teaches away from  
Applicants' invention. Specifically, Mullis teaches:



1 The present invention obviates the need for  
2 extensive purification of the product from a  
3 complicated biological mixture.

4 (Col. 2, lines 32-34). Mullis reaffirmed this teaching later in the  
5 disclosure:

6 *It is not necessary that the sequence to be*  
7 *amplified be present initially in a pure form; it*  
8 *may be a minor fraction of a complex mixture ...*  
9 *or a portion of a nucleic acid sequence due to a*  
10 *particular microorganism which organism might*  
11 *constitute only a very minor fraction of a*  
12 *particular biological sample.*

13 (Col. 5, lines 49-56). Plainly, Mullis teaches that the amplification  
14 method of his invention does not include purification before  
15 amplification and, in fact, does not require purification. Thus,  
16 Mullis teaches away from Applicants' invention.

17 12/5/95 Preliminary Amendment at p. 16 [emphasis added]. The applicants repeated this  
18 representation to the Patent Office regarding the teachings of Mullis in the Amendment filed on  
19 October 18, 1996, at pp. 11-12.

20 203. The paragraph cited by the applicants from the Mullis patent reads in whole:

21 Any source of nucleic acid, in *purified* or nonpurified form, can be  
22 utilized as the starting nucleic acid or acids, provided it contains or  
23 is suspected of containing the specific nucleic acid sequence  
24 desired. Thus, the process may employ, for example, DNA or  
25 RNA, including *messenger RNA*, which DNA or RNA may be  
26 single stranded or double stranded. In addition, a DNA-RNA  
27 hybrid which contains one strand of each may be utilized. A  
28 mixture of any of these nucleic acids may also be employed, or *the*  
*nucleic acid produced from a previous amplification reaction*  
herein using the same or different primers may be so utilized. The  
specific nucleic acid sequence to be amplified may be only a  
fraction of a larger molecule or *can be present initially as a*  
*discrete molecule, so that the specific sequence constitutes the*  
*entire nucleic acid. It is not necessary that the sequence to be*  
*amplified be present initially in a pure form; it may be a minor*  
*fraction of a complex mixture*, such as a portion of the .beta.-  
globin gene contained in whole human DNA or a portion of  
*nucleic acid sequence due to a particular microorganism which*  
*organism might constitute only a very minor fraction of a*  
*particular biological sample.* The starting nucleic acid may contain

1 more than one desired specific nucleic acid sequence which may  
2 be the same or different. Therefore, the present process is useful  
3 not only for producing large amounts of one specific nucleic acid  
4 sequence, but also for amplifying simultaneously more than one  
different specific nucleic acid sequence located on the same or  
different nucleic acid molecules.

5 (Col. 5, lines 34-63), emphasis added, underlined is the portion selectively cited by the applicants).  
6 Thus, contrary to the applicants' representation to the Patent Office, the omitted portion of the  
7 paragraph cited by the applicants expressly teaches that purification combined with the  
8 amplification invention was disclosed in the art, thereby validating the Examiner's rejection.

9 **204.** In addition to the excluded portion of the paragraph of the Mullis patent, the very  
10 next paragraph in the Mullis patent states:

11 The nucleic acid or acids may be obtained from any source, for  
12 example, from plasmids such as pBR322, from cloned DNA or  
13 RNA, or from natural DNA or RNA from any source, including  
14 bacteria, yeast, viruses, and higher organisms such as plants or  
15 animals. *DNA or RNA may be extracted from blood, tissue  
16 material such as chorionic villi or amniotic cells by a variety of  
techniques such as that described by Maniatis et al., Molecular  
Cloning A Laboratory Manual (New York: Cold Spring Harbor  
Laboratory, 1982), pp. 280-281.*

17 (Col. 5, line 64-col. 6, line 6 [emphasis added]). Maniatis, et al., is a methods manual that teaches a  
18 variety of techniques for purifying RNA or DNA from blood, tissue or other cellular material. At  
19 pages 197-198 of Maniatis, et al., this reference teaches the purification of mRNA on a solid  
20 support using a probe. Thus, the very next paragraph of the Mullis patent following the selective  
21 citation by the applicants incorporates a disclosure of *how* to purify a nucleic acid from a sample  
22 prior to amplification. The applicants' selective removal of the first half of the cited paragraph that  
23 fully supported the Examiner's rejection based on Mullis and the following paragraph's implicit  
24 teaching of how to purify a nucleic acid from a sample prior to amplification evidence the knowing  
25 and intentional nature of the applicants' misrepresentation of the Mullis reference.

26 **4. Applicant's Misrepresentations In Connection With The Request for**  
27 **Certificate of Correction Filed for the '338 Patent**

28 **205.** By the December 14, 1998, Request for Certificate of Correction, the applicants

1 intentionally misrepresented to the Patent Office that the prior intentional choices made by patent  
2 counsel as to which "correction" was sought were "mistakes" and that those mistakes were of  
3 "minor character." The applicants knew that the true facts were that intentional choices by patent  
4 counsel were not "mistakes" under applicable law and that defects which rendered the '338 patent  
5 invalid could not constitute mistakes "of minor character."

6       **206.** By the December 14, 1998, Request for Certificate of Correction the applicants  
7 attempted to cure fatal defects in the '338 patent by, among other things, intentionally  
8 misrepresenting to the Patent Office that the prior intentional choices made by patent counsel as to  
9 which "correction" was sought resulted from errors made in good faith by the applicants. The  
10 applicants knew that the true facts were neither the request for certificate of correction nor any act  
11 after the abandonment of the '505 application was undertaken by applicants in good faith.

12       **207.** By the December 14, 1998, Request for Certificate of Correction, the applicants  
13 attempted to cure fatal defects in the '338 patent by, among other things, intentionally  
14 misrepresenting to the Patent Office when applicants had discovered the mistakes as to which  
15 correction was sought. The applicants knew that the true facts were that defects had been  
16 discovered earlier than they disclosed to the Patent Office. Applicants and their counsel  
17 represented that the so-called "Error 2" only recently been identified, when in fact they knew that  
18 "Error 2" had been identified in 1995 and an amendment requested on March 8, 1995 in the course  
19 of the prosecution of application 08/400,657.

20       **208.** By the December 14, 1998, Request for Certificate of Correction, the applicants  
21 attempted to cure fatal defects in the '338 patent by, among other things, intentionally  
22 misrepresenting to the Patent Office that the '505 application had been inadvertently and  
23 unintentionally abandoned. The applicants made this representation knowing that the true facts  
24 were that the '505 application was intentionally abandoned.

25       **209.** The applicants further represented in the Request for Certificate of Correction for  
26 the '338 patent that the '338 patent was a continuation of the '826 application. However, the '338  
27 patent could not be a continuation of the '826 application, because the disclosure of the '338 patent  
28 was not identical to the disclosure of the '826 application.

1           **210.** The applicants knew that the '338 patent could not be a continuation of the '826  
2 application, and that through the aforementioned Certificate of Correction, the applicants  
3 knowingly and intentionally misrepresented their knowledge with the intent of deceiving the U.S.  
4 Patent and Trademark Office.

5           **211.** The misrepresentations of applicants set forth herein were material. As a direct  
6 result of the conduct of applicants set forth herein, the certificate of correction was entered by the  
7 Patent Office on September 7, 1999.

8                   **5. Applicants' Misrepresentation in their Petition under 37 C.F.R. §1.182**

9           **212.** The applicants misrepresented legal authority to the Patent Office in their  
10 December 14, 1998 petition under 37 C.F.R. § 1.182, in that that they knew that the legal authority  
11 presented to the Patent Office to support the petition to amend the '826 application and cure the  
12 otherwise fatal priority defect in the '338 patent did not stand for the proffered proposition and that  
13 the applicants knowingly misrepresented this legal authority to the Patent Office with the intent to  
14 deceive the Patent Office.

15           **213.** In petitioning to amend the three abandoned applications, applicants did not  
16 disclose to the PTO that they were seeking to circumvent applicants' abandonment of the '505  
17 application nor did they even disclose the existence of that prior application.

18           **214.** In petitioning in December 1998 to amend the three abandoned applications,  
19 applicants did not disclose to the PTO that they had discovered the defect they sought to amend no  
20 later than March 8, 1995 and that an amendment had been requested to the '657 application on that  
21 date.

22           **215.** As direct result of the conduct of applicants set forth herein, the petitions to amend  
23 the abandoned applications were granted by the PTO in a decision mailed July 1, 1999.

24                   **6. Applicants' Failure to Disclose The Known Inoperativeness of their**  
25                   **Exponential Non-specific Amplification Techniques**

26           **216.** In their specification, applicants' purported to describe two exponential non-  
27 specification amplification techniques. Example 6, for example, purports to describe a scheme for  
28 exponential non-specific amplification using random hexamer primers whereas Example 7

1 purports to describe the use of Q $\beta$  replicase to exponentially amplify target nucleic acids. Both  
2 examples are written in "prophetic" form suggesting that Vysis had not actually attempted to  
3 reduce either of those examples to practice.

4       **217.** As to Example 6, any suggestion that Vysis had not sought to reduce that invention  
5 to practice prior to the filing date of the '920 application is false. In reality, a team of Gene Trak  
6 scientists including Dr. Scott Decker struggled for months prior to the December 21, 1987 filing  
7 date of the '920 application to attempt to practice the technique disclosed in Example 6 before  
8 ultimately concluding that Example 6 would not result in amplification of a target polynucleotide.  
9 Gene Trak never achieved amplification using the technique disclosed in Example 6.

10       **218.** As to Example 7, neither Gene Trak nor Vysis ever attempted to implement this  
11 Example. Gen-Probe believes that at the time of filing of the '920 application, Vysis had no  
12 reasonable expectation that Example 7 was then operative or would ever become operative due to  
13 the highly specific nature of the Q $\beta$  replicase enzyme.

14       **219.** The applicants for the '338 patent had a duty to disclose the foregoing material facts  
15 of inoperativeness to the Examiner. Particularly where those facts were known prior to filing, the  
16 applicants had a duty to disclose that they had already attempted and failed to practice their  
17 prophetic examples.

18       **G. THE '338 PATENT IS UNENFORCEABLE ON THE GROUND OF LACHES**

19       **220.** The foregoing discussion of the prosecution history of the '338 patent demonstrates  
20 that the applicants intentionally, unreasonably, and inexcusably delayed in the prosecution of the  
21 invention claimed in the '338 patent.

22       **221.** Vysis unreasonably and without explanation delayed the prosecution of the  
23 applications for the inventions claimed in the '338 patent from the filing of the 136,920  
24 application on December 21, 1987 through at least the issuance of the patent on May 12, 1998, a  
25 period of 10½ years.

26       **222.** Vysis delayed the prosecution of applications for the inventions claimed in the '338  
27 patent unreasonably and without explanation by (among other things) obtaining extensions of time  
28 to respond to office actions by the Patent Office, failing to respond on the merits to such office

actions by the Patent Office and instead abandoning patent applications while under rejection and filing continuation applications. Vysis repeated this practice many times over the 10½-year period in which the claims of the '338 patent were prosecuted.

223. Additionally, Vysis delayed the prosecution of its claims by improper and untimely claims of priority, including but not limited to contending that the '080 application was a divisional of '757 application, the improper claim that the '080 application was a continuation of the '826 application, and the delay in contending that the '080 application was a continuation of the '826 application.

224. Gen-Probe denies that the '338 patent encompasses any of Gen-Probe's products. Alternatively, however, if the '338 patent covers Gen-Probe products, Gen-Probe contends that it was injured by Vysis' unreasonable and unexplained delay in prosecuting applications for the inventions claimed in the '338 patent. These injuries include Vysis obtaining extended patent protection for the inventions claimed in the '338 patent by delaying issuance of the patent. Additionally, during the period of time that the prosecution was delayed, Gen-Probe made numerous product design and product development decisions with respect to technologies related to, but neither the same as or equivalent to, those claimed in the '338 patent.

#### H. VYSIS ABANDONED THE INVENTIONS CLAIMED IN THE '338 PATENT.

225. As set forth above, on February 5, 1993, the applicants intentionally abandoned U.S. patent application 07/944,505 with full knowledge of their rights. Applicants thereafter, intentionally and with full knowledge of their rights, took no further action with respect to prosecuting claims for the inventions that had been the subject of the '505 application until May 3, 1994. Applicants elected this course of action (and inaction) in response to rejections by the Patent Office of the '920, '967, and '505 applications, of which certain of the office actions were first action final rejections. Applicants took this action, in part, in response to fiscal constraints imposed at the time on Vysis. Applicants' abandonment of the '505 application and subsequent inaction establish that applicants abandoned the inventions claimed therein in the United States.

#### I. VYSIS HAS COMMITTED ACTS OF UNFAIR COMPETITION

226. Based on the facts relating to the scope, invalidity and unenforceability of the '338

1 patent, as described above, Vysis knew or should reasonably have known that these facts establish  
2 that the claims of the '338 patent are invalid and/or unenforceable and do not cover Gen-Probe's  
3 TMA blood screening assay. In the first half of 1999, Vysis repeatedly asserted, orally and in  
4 writing, that Gen-Probe's TMA blood screening assay was encompassed by the claims of the '338  
5 patent. By asserting that the claims of the '338 patent were valid and covered Gen-Probe's NAT  
6 products and by requiring Gen-Probe to take a license thereto in order to avoid litigation, Vysis  
7 acted, and continues to act, unfairly, inequitably and in bad faith.

8       **227.** Vysis' actions constitute unlawful, unfair or fraudulent business practices under  
9 California Business & Professions Code Sections 17200, *et seq.*

### 10   **III. CONTENTIONS OF LAW**

#### 11       **A. GEN-PROBE'S PRODUCTS DO NOT INFRINGE THE '338 PATENT**

12       **228.** It is unlawful to make, use, offer to sell, or sell any patented technology, within the  
13 United States, or import into the United States any patented invention during the term of the patent  
14 without authorization from the patent owner. 35 U.S.C. § 271. Gen-Probe is licensed by Vysis  
15 under the '338 patent, and hence, cannot technically infringe the claims of the '338 patent.  
16 Nevertheless, Gen-Probe brought this action believing that, notwithstanding the license granted to  
17 it by Vysis, Gen-Probe is entitled to a judgment that its blood screening products do not infringe  
18 any valid claim of the '338 patent.

19       **229.** By virtue of its Order dated June 20, 2001, the Court has already entered judgment  
20 in favor of Gen-Probe adjudging that Gen-Probe does not literally infringe the claims of the '338  
21 patent on the basis of the Court's construction of the term "amplifying" the target polynucleotide  
22 to include only methods of non-specific amplification. Thus, the only remaining issue relating to  
23 non-infringement is whether Gen-Probe's blood screening products infringe the claims of the '338  
24 patent under the Doctrine of Equivalents.

25       **230.** As the patent owner, Vysis bears the burden of proof with respect to infringement.  
26 Vysis must establish by a preponderance of the evidence that Gen-Probe's products infringe a  
27 valid claim of the '338 patent under the Doctrine of Equivalents.

28       **231.** Vysis asserts that, absent the existence of the parties' license, Gen-Probe would

1 infringe claims 1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 13, 14, 24 and 25 of the '338 patent. Gen-Probe denies  
2 these allegations.

3       **232.** Claims 1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 13 and 14 are method claims that are technically  
4 infringed in the first instance, if at all, by Gen-Probe's customers that actually perform the  
5 diagnostic methods enabled by Gen-Probe's kits.

6       **233.** Gen-Probe's infringement exposure for technical infringement of the forgoing  
7 method claims is thus focused on its alleged liability for inducing "technical" infringement by  
8 Gen-Probe's customers who use the Gen-Probe NAT kits in accordance with the instructions and  
9 protocols Gen-Probe provides with those diagnostic kits.

10       **234.** Claims 24 and 25 of the '338 patent are kit claims that are written in "means-plus-  
11 function" format. In order for Vysis to prove literal infringement of those means-plus-function  
12 claims, Vysis would have had to show that the elements of Gen-Probe's kits perform the identical  
13 function to the function recited in the claims. The Court has previously held that these claims are  
14 not literally infringed because specific amplification techniques like TMA and PCR do not  
15 perform the identical function of the amplification means disclosed in the '338 patent. However,  
16 even if Vysis could have established that Gen-Probe's products perform the identical function of  
17 the "amplification means"— which it cannot, it would also have to show that Gen-Probe's kit  
18 elements use the same structure or materials described in the specification, or their equivalents.

19       **235.** Because the individual elements and techniques employed in Gen-Probe's products  
20 were generally known and used prior to the filing date of the '920 application (and certainly prior  
21 to the '080 application), Vysis is not entitled to seek a still further equivalents analysis as to  
22 Claims 24 and 25. *See Chiuminatta Concrete Concepts, Inc. v. Cardinal Indus., Inc.*, 145 F.3d  
23 1303, 1311 (Fed. Cir. 1998). In other words, because the general technology and components used  
24 in Gen-Probe's accused products consisted of elements known or anticipated in December 1987  
25 (and certainly by May 1994 – the date of filing for the '080 application), Vysis is not entitled to an  
26 "equivalent of a equivalent" inquiry. *See id.* ("[G]iven the prior knowledge of the technology  
27 asserted to be equivalent, it could readily have been disclosed in the patent. There is no policy  
28 based reason why a patentee should get two bites of the apple.").



236. As to claims 1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 13 and 14, in order to establish infringement under the doctrine of equivalents the patent owner must prove that the differences between the claim element at issue and the corresponding element in the accused product are “insubstantial.” *Warner-Jenkinson v. Hilton-Davis Chemical Co.*, 520 U.S. 17, 28-30 (1997); *Gamma-Metrics Inc. v. Scantech Ltd.*, 52 USPQ2d 1568, 1574 (S.D. Cal. 1998) (Huff, J.). The issue is frequently determined by asking whether the accused product “performs the same function, in the same way, to achieve the same result” as the claim element at issue. *Warner-Jenkinson*, 520 U.S. at 39; *Gamma-Metrics Inc.*, 52 USPQ2d at 1574. Under the “all elements” rule, each element contained in a patent claim is deemed material to defining the scope of the patented invention, and thus each individual element of the claim must be considered, *not the invention as a whole*. *Warner-Jenkinson Co.*, 520 U.S. at 29-30; *Loral Fairchild Corp. v. Sony Corp.*, 181 F.3d 1313, 1322 1327 (Fed. Cir. 1999); *Gamma-Metrics Inc.* 52 USPQ2d at 1574. Thus the “function-way-result” comparison of the accused product to the patent claim must be made on an element-by-element basis. *Stryker Corp. v. Davol Inc.*, 10 F.Supp.2d 841, 845 (W.D. Mich. 1998).

237. As set forth in the factual discussion in Section II, above, the facts show that substantial differences exist between generic forms of specific amplification and non-specific amplification, when considered as separate elements and when considered in the “context of the claims” under the “all elements rule.” TMA does not perform substantially the same function in substantially the same way to achieve substantially the same result as the non-specific methods of amplification literally encompassed by the claims of the ‘338 patent.

238. Specific amplification does *not* perform the same function, in the same way, to achieve the same result as non-specific amplification. The inventors and other employees of Gene-Trak/Vysis admitted that these methods were “different” and further admitted that non-specific amplification was the “opposite” of specific amplification. The text of the ‘338 patent specification itself admits and highlights the differences between the two methods of amplification:

Amplification of the target nucleic acid sequences, because it follows purification of the target sequences, can employ non-specific enzymes or primers (i.e., enzymes or primers which are capable of causing the replication of virtually any nucleic acid sequence).

1 Although any background, non-target, nucleic acids are replicated  
2 along with target, this is not a problem because most of the  
3 background nucleic acids have been removed in the course of the  
4 capture process. *Thus, no specially tailored primers are needed for  
5 each test, and the same standard amplification reagents can be used,  
6 regardless of the targets.*

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[ '338 Patent, at 30:38-40 (emphasis added).] This statement provides an admission of the  
substantial differences between non-specific and specific amplification:

- that non-specific amplification utilizes non-specific enzymes or primers "(i.e., enzymes or primers which are capable of causing the replication of virtually any nucleic acid sequence)."
- that with non-specific amplification the "same standard amplification reagents can be used, regardless of the targets."
- that non-specific amplification results in "background, non-target, nucleic acids [being] replicated along with target."

*Id.* By differentiating between non-specific and specific amplification in that manner, thus teaching away from the use of specific primers and enzymes, the '338 patent forecloses any possibility that Gen-Probe's TMA method could be considered equivalent to the claimed non-specific amplification techniques. *See Spectra Corp. v. Lutz*, 839 F.2d 1579, 1582 (Fed. Cir. 1988) (clear and uncontroverted statements in patent specification precluded contrary argument of equivalence); *Brenner v. United States*, 773 F.2d 306, 308 (Fed. Cir. 1985).

239. Not only is the *general* technique of TMA significantly different from the claimed non-specific amplification techniques of the '338 patent but the particular embodiment of TMA the Gen-Probe has deployed in its accused products represents an even more distinguishable basis for rejecting a claim of infringement under the Doctrine of Equivalents. Vysis has not attempted to analyze Gen-Probe's specific embodiments and therefore cannot meet its burden of proof on this issue.

240. Finally, the fact that Gen-Probe's products are encompassed by independent patents issued by the United States Patent Office over the express reference to the '338 patent provides additional evidence to substantiate the lack of equivalence between Gen-Probe's products and the claims of the '338 patent. Although this fact of independent patentability is not conclusive, it provides persuasive proof of the substantial differences between Gen-Probe's products.

1                   **1. Other Issues**

2           **241.** The Court's summary judgment order on literal infringement greatly reduces the  
3 number of claim construction issues remaining to be resolved. Several issues remain for purposes  
4 of invalidity and infringement analysis, however, such as claim scope in connection with  
5 evaluating whether certain prior art anticipates the claims of the '338 patent. The remaining claim  
6 interpretation issues may be resolved by the Court prior to or during the course of trial in  
7 accordance with *Markman v. Westview Instruments, Inc.* 52 F.3d 967 (Fed. Cir. 1995), *aff'd*, 517  
8 U.S. 370 (1996). The issues are identified and discussed below.

9           **242.** "*Amplifying the Target Polynucleotide.*" Each of the claims asserted by Vysis to be  
10 infringed by Gen-Probe's products contains the term "amplifying". As noted above, the Court has  
11 already construed the meaning of the term "amplifying" to mean making copies of a target  
12 polynucleotide by using methods of non-specific amplification. (June 20, 2001 Order).  
13 Additional issues of claim interpretation remain.

14           (a) For example, Gen-Probe contends that "amplifying the target  
15 polynucleotide" includes indirect methods of target amplification, such as by creating an  
16 amplification product such as reporter molecules, *i.e.*, "target-like molecules which are capable of  
17 functioning in a manner like the target molecule, or a molecule subject to detection steps in place  
18 of the target molecule, which molecules are created by virtue of the of the presence of the target  
19 molecule in the sample." ('338 patent at col. 2, ll. 9 – 15.)

20           (b) Gen-Probe further contends that "amplifying the target polynucleotide"  
21 includes both *in vitro* and *in vivo* amplification methods. Amplification methods do not need to  
22 be useful in a commercial diagnostic kit in order to be included within the scope of the '338 patent  
23 claims.

24           (c) Gen-Probe further contends that "amplifying" does not include mere  
25 synthesis of a nucleotide sequence complementary to a sequence in the target.

26           (d) "*A First Support.*" Claims 1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 13, and 14 are  
27 asserted by Vysis as being infringed by Gen-Probe. Each of these claims requires the use of a first  
28 support that binds to the target polynucleotide. Gen-Probe contends that the term "support" as

1 used in these claims includes all types of solid phases, including conventional supports such as  
2 filters, membranes, and absorbents used in column chromatography or batch separations. For  
3 example, the term "support" as used in these claims includes nitrocellulose, oligo(dT) cellulose,  
4 hydroxyapatite, streptavidin agarose, and magnetic beads with covalently attached capture  
5 oligonucleotides. The term "support" includes solid phases that bind non-specifically as well as  
6 specifically with the target polynucleotide. Supports do not need to be useful in a commercial  
7 diagnostic kit in order to be included within the scope of the '338 patent.

8       **243.** *"A First Support Which Binds to the Target Polynucleotide."* Claims 1, 2, 3, 4, 5, 7,  
9 8, 9, 10, 11, 13, and 14 are asserted by Vysis as being infringed by Gen-Probe. Each of these  
10 claims requires the use of "a first support which binds to the target polynucleotide." Certain of  
11 these claims require the first support to include "a probe which binds with the target  
12 polynucleotide." To the extent that the term "binds" is construed to mean "a direct attachment"  
13 between the first support or probe and the target nucleic acid, then Gen-Probe's products do not  
14 employ such a step. (This definition of "a direct attachment" is consistent with the definition of  
15 "bind" set forth in The American Heritage Dictionary of the English Language as "to cause to  
16 cohere or stick together in a mass.") Gen-Probe's products employ a procedure whereby a capture  
17 probe first binds to the target nucleic acid to form a capture probe-target complex. The capture  
18 probe then binds to an intermediary probe that is attached to a solid support. Neither the support  
19 nor the support-bound probe bind directly to the target.

20       **244.** Because the Gen-Probe products do not employ a direct binding procedure whereby  
21 the capture probe directly binds to a solid support, the Gen-Probe products also do not literally  
22 infringe the '338 patent for this further reason. In addition, the Gen-Probe products do not infringe  
23 these claims under the doctrine of equivalents for the reasons set forth in greater detail in the  
24 specification of Gen-Probe's patent, United States Patent No. 6,110,678 (the '678 patent"). The  
25 absence in Gen-Probe's products of the required direct binding step results in significant and  
26 functional differences from the techniques disclosed in the '338 patent.

27       **245.** *"Means for Amplifying the Target Polynucleotide."* As noted above, Vysis asserts  
28 that claims 24 and 25 are infringed by Gen-Probe's products. Claims 24 and 25 are directed to a

1 "kit" for amplifying a target polynucleotide, and these claims use the term "means for amplifying  
2 the target polynucleotide." Claim elements drafted in language that merely claims a means for  
3 performing a specified function without further reciting the structure, material or acts in support of  
4 that means are classified as means-plus-function limitations, which are subject to 35 U.S.C. § 112,  
5 paragraph 6. In order to literally meet a means-plus-function limitation, "an accused device must  
6 (1) perform the identical function recited in the means limitation and (2) perform that function  
7 using the structure disclosed in the specification or an equivalent structure." *Carroll Touch, Inc. v.*  
8 *Electro Mechanical Systems, Inc.*, 15 F.3d 1573, 1578 (Fed. Cir. 1993); *see also Cybor Corp. v.*  
9 *FAS Technologies, Inc.*, 138 F.3d 1448, 1457 (Fed. Cir. 1998) ("Under § 112, ¶ 6, an accused  
10 device with structure not identical to the structure described in the patent will literally infringe the  
11 patent if the device performs the identical function required by the claim with a structure  
12 equivalent to that described in the patent.")

13       **246.** The only "structures" disclosed in the specification of the '338 patent to perform  
14 the function of "amplification" are the non-specific amplification techniques disclosed in  
15 Examples 4, 5, 6 and 7. Based upon the Court's June 20, 2001 Order construing the term  
16 "amplification," claims 24 and 25 can be literally infringed only by a structure that performs the  
17 identical function as that provided by the non-specific amplification enzymes and primers  
18 disclosed in the '338 patent and that represents the same or equivalent structure as those non-  
19 specific enzymes and primers. *Carroll Touch*, 15 F.3d at 1578. Inasmuch as the inventors' stated  
20 purpose in using non-specific primers and enzymes was to find an amplification technique that was  
21 different and presumably non-interchangeable with PCR as well as to simplify and reduce the cost  
22 of design and manufacture of amplification reagents so as to allow for the use of amplification  
23 reagents that would perform the function of amplifying any nucleic acids present in a sample  
24 medium, Gen-Probe's TMA method, in general and as specifically deployed in its accused  
25 products, does not perform this identical function. Rather, Gen-Probe's products are specifically  
26 designed to perform a significantly different function, that being the amplification of only the  
27 desired target nucleic acid.

28       **247.** *The Order of the Capture, Amplification, and Detection Steps.* Each of the claims

recites steps that include capture on a solid support and non-specific amplification. The claims do not require that the steps be performed in any particular order to be included within the scope of the patent. Unless the steps of a method actually recite an order, the steps are not ordinarily construed to require one. *Interactive Gift Express Inc. v. Compuserve Inc.*, 256 F.3d 1323, 1342 (Fed. Cir. 2001). Three of the four preferred embodiments sets forth in the '338 patent use a capture step both before and after amplification. Thus, prior art is relevant to the issues of obviousness and anticipation as to the '338 patent if such art discloses amplification and capture on a solid support, regardless of the order in which those steps are performed.

## **B. THE '338 PATENT IS INVALID**

### **1. Lack of Enablement**

#### **a. Enablement requires that the specification teach those skilled in the art how to make and use the *full scope* of the claimed invention without "undue experimentation."**

248. Paragraph 1 of Section 112 of the Patent Act requires that the specification of each patent "shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains . . . to make and use the same . . . ." 35 U.S.C. § 112, ¶ 1. The patent's teachings must be commensurate in scope with the breadth of the claim: "[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the *full scope* of the claimed invention without 'undue experimentation.'" *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997) (citations omitted; emphasis added). Indeed, "[t]he scope of the claims must be less than or equal to the scope of the enablement." *Nat'l Recovery, Inc. v. Magnetic Separation Sys., Inc.*, 166 F.3d 1190, 1196 (Fed. Cir. 1999).

249. The scope of enablement, in turn, "is that which is disclosed in the specification plus the scope of what would be known to one of ordinary skill in the art without undue experimentation." See also *In re Goodman*, 11 F.3d 1046, 1050 (Fed. Cir. 1993) ("the specification must teach those of skill in the art 'how to make and how to use the invention as broadly as it is claimed'"). One purpose of the enablement requirement is fairness – a patentee is not allowed to claim more than what is taught by the patent. *Nat'l Recovery*, 166 F.3d at 1195-96.

1 There must be sufficient disclosure, either through illustrative examples or terminology, to teach  
2 those of ordinary skill how to make and use the invention as broadly as it is claimed. *Enzo*  
3 *Biochem, Inc., v. Calgene, Inc.*, 188 F.3d 1362, 1374 (Fed. Cir. 1999); *In re Vaeck*, 947 F.2d 488,  
4 496 & n.23 (Fed. Cir. 1991).

5       **250.** Whether claims are sufficiently enabled by a disclosure in a specification is  
6 determined as of the date that the patent application was first filed. *Enzo Biochem, Inc.*, 188 F.3d  
7 at 1374.

8       **251.** A patent specification is not enabling when it does no more than suggest a “plan” or  
9 state an “invitation” for those of skill in the art to experiment using suggested methods, but does  
10 not provide sufficient guidance or specificity as to how to execute that plan. *Genentech, supra*,  
11 108 F.3d at 1366.

12       **252.** A number of factors may be considered in determining whether a disclosure would  
13 require “undue experimentation.” These factors are as follows:

14               the quantity of experimentation necessary;  
15               the amount of direction or guidance presented;  
16               the presence or absence of working examples;  
17               the nature of the invention;  
18               the state of the prior art;  
19               the relative skill of those in the art;  
20               the predictability or unpredictability of the art; and  
21               the breadth of the claims.

22 *Enzo Biochem, Inc., supra*, 188 F.3d at 1374. Not all of the factors need to be reviewed when  
23 determining whether a disclosure is enabling. *Id.*

24       **253.** The required scope of enablement of the specification varies inversely with the  
25 degree of unpredictability in the art. *In re Angstadt*, 537 F.2d 498, 502 (C.C.P.A. 1976). For  
26 claimed inventions in the biological arts, the required level of disclosure is much greater than, for  
27 example, the disclosure that would be required of an invention involving a “predictable” factor  
28 such as a mechanical or electrical element. *Enzo Biochem, Inc., supra*, 188 F.3d at 1374; *In re*  
*Vaeck, supra*, 947 F.2d at 496; 3 Donald S. Chisum, Chisum on Patents, § 7.03[4][d][i], at 7-58  
(1999). The invention claimed in the ‘338 patent of methods of target capture and amplification of  
nucleic acids clearly falls within the unpredictable biological arts. As such, if a patentee’s claims

are sufficiently broad to encompass all possible permutations of an element, then the disclosure of one embodiment will not be sufficient. *Id.*, see also *In re Goodman*, 11 F.3d 1046, 1050 (Fed. Cir. 1993); *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.3d 1200, 1213-14 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991).

b. The '338 patent claims necessarily encompass all manner of non-specific amplification, particularly including exponential amplification as set forth in Examples 6 and 7, and must encompass any type and sequence of nucleic acid.

254. As construed by this Court, the claim term "amplifying" of the '338 patent covers non-specific amplification:

Based on the explicit language of the specification, the repeated references to non-specific amplification methods, and the absence of any reference to specific amplification or PCR, the Court construes the term "amplifying" as found in the claims of the '338 patent to encompass only non-specific amplification. The Court finds that one of ordinary skill in the art as of December 1987 would have understood from the specification that the inventors' method combined target capture and non-specific amplification.

[June 20, 2001 Order at 10.] For the same reasons that compel the conclusion that the term "amplifying" is limited to non-specific amplification, that term also includes all manner of practice of that generic technique.

255. As noted in Section II, above, Examples 6 and 7 represent at least two of the inventors' preferred embodiments of non-specific amplification claimed in the patent. Because they represent preferred embodiments, the non-specific amplification techniques they purport to disclose are presumed to be encompassed within the scope of the amplification term of the claims. *Vitronics Corp. v. Conceptiontronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996).

256. In *Vitronics*, the Federal Circuit held that patent claims must be construed consistently with the specification and the preferred embodiments described therein. *Vitronics*, supra, 90 F.3d 1576, 1583. Indeed, the Federal Circuit has held that a claim interpretation in which a preferred embodiment would not fall within the scope of a patent claim "is rarely, if ever, correct and would require highly persuasive evidentiary support . . . ." *Id.*; accord, *Moline Mfg. Co. v. United States Int'l Trade Comm'n*, 75 F.3d 1545, 1550 (Fed. Cir. 1996). As the Court in



1 Moline stated, "it is unlikely that an inventor would define the invention in a way that excluded the  
2 preferred embodiment, or that persons of skill in this field would read the specification in such a  
3 way." *Id.* at 1550.

4 257. Similarly, the doctrine of claim differentiation provides independent confirmation  
5 that the inventors meant to include all of the examples of non-specific amplification within the  
6 scope of the "amplification term." Briefly stated, the doctrine of claim differentiation provides  
7 that the construction of the language in one claim of a patent must be undertaken with appropriate  
8 consideration to the language in the other claims of the patent. See *e.g.*, *Chisum on Patents*, §  
9 18.03[6]. One corollary of the doctrine helps confirm that an otherwise unrestricted independent  
10 claim necessarily encompasses greater breadth than a restricted dependent claim.

11 258. With respect to the '338 patent, dependent claim 5 claims the use of Q $\beta$  replicase as  
12 the claimed amplification polymerase. However, the only embodiment that describes the use of  
13 the Q $\beta$  replicase enzyme as an amplification polymerase is Example 7. As such, the inventors  
14 must have intended to encompass Example 7, among others, within the scope of dependent claim  
15 5. In turn, based upon the doctrine of claim differentiation, one of ordinary skill would also  
16 conclude that claim 4, from which claim 5 depends, and claim 1, from which claim 4 depends,  
17 encompass at least Example 7 and, in the absence of any other limitation, would also encompass  
18 all the other preferred embodiments, including Example 6.

19 259. Thus, because the claims encompass *at least* Examples 6 and 7, and indeed are  
20 broader than these embodiments, the Court should construe the "amplification" term of the claims  
21 of the '338 patent to encompass the full extent of the described and illustrated non-specific  
22 amplification techniques. In conjunction with the Court's June 20<sup>th</sup> construction, Gen-Probe  
23 submits that the Court should construe that term as follows:

24 the term "amplifying" as found in the claims of the '338 patent  
25 encompass only non-specific amplification. Within the general  
26 category of non-specific amplification, the term further includes all  
27 manner of implementation of that technique including, but not  
28 limited to the disclosed techniques described in Examples 4, 5, 6 and  
7 of the specification. The Court finds that one of ordinary skill in  
the art as of December 1987 would have understood from the  
specification that the inventors' method combined target capture and  
all manner of non-specific amplification, including the disclosed

examples.

260. Gen-Probe further submits that the Court should construe the term “amplification” as used in the ‘338 patent to encompass only the process of creating multiple double-stranded copies of the target polynucleotide or multiple transcripts made from a double-stranded and not to include the mere creation of a single complementary transcript copy of a target strand.

**c. “Target Polynucleotide” of the Claims Encompasses DNA and RNA of any desired sequence.**

261. The ‘338 patent describes a target polynucleotide as either DNA or RNA, having a base sequence of particular interest indicative of pathogens, genetic conditions, or desirable gene characteristics.” (‘338 patent, col. 2; l. 59 – col. 3, l. 5.) Again, without further limitation, that term should be given its defined meaning without restriction to any particular sequence or type of nucleic acid. *See, e.g., Vitronics Corp. supra*, 90 F.3d at 1582.

**d. As properly construed, the claims of the ‘338 patent encompassing non-specific amplification of any desired sequence of DNA or RNA are invalid for lack of enablement.**

**The specification does not enable the full breadth of the claims.**

262. Section 112 requires that a patent’s teachings must be commensurate in scope with the breadth of each claim. *See e.g., Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997). Logically, therefore, the scope of the claims must be less than or equal to the scope of the enablement; otherwise, the claims are invalid. *See, e.g., Nat’l Recovery*, 166 F.3d at 1196.

263. The evidence in this case that shows that the inventors and their colleagues did not – and could not – enable the successful practice of the non-specific exponential amplification techniques of Examples 6 and 7. Similarly, the evidence in this case that shows that the inventors and their colleagues did not – and could not – enable the successful practice of the non-specific linear amplification techniques of Examples 4 and 5.

264. As set forth above, by the claimed filing date of the disclosure of the invention on December 21, 1987, Gene Trak scientists had not successfully performed the non-specific amplification technique disclosed in Example 6. Despite over 5 months of dedicated effort, those

1 skilled scientists, who met or exceeded the level of ordinary skill, concluded that the technique  
2 simply would not work. Because they were using far more detailed methods and techniques than  
3 disclosed in Example 6, clearly the specification failed to provide the necessary teaching to satisfy  
4 Section 112. Because inventors are presumed to possess insight or knowledge beyond the  
5 "conventional wisdom" possessed by a person of ordinary skill in the art, *Standard Oil Co. v.*  
6 *American Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985), Gene Trak's undisclosed internal  
7 failure to perfect Example 6 is powerful evidence of its lack of enablement.

8       **265.** As to Example 7, to this day, no scientist from either Gene Trak or Vysis has ever  
9 even attempted this technique. Given the great scientific and commercial value that would derive  
10 from any successful implementation of this claimed technique, their absolute failure to pursue their  
11 own alleged invention speaks volumes as to the reason for that lack of effort.

12       **266.** Vysis also cannot dispute that the mere disclosure of Blumenthal's prior art paper  
13 does not provide sufficient teaching to enable the practice of either linear or exponential  
14 amplification techniques of Example 7 across the full spectrum of potential target polynucleotide  
15 sequences. As noted above, that paper merely confirms the extensive experimentation required to  
16 achieve even partial copying of a few selected nucleic acids. Blumenthal does not provide a  
17 disclosure sufficient to enable even linear amplification across the full spectrum of claimed nucleic  
18 acids and provides no teaching whatsoever of the claimed use of Q $\beta$  replicase for exponential  
19 amplification. Indeed, to this day, there are no published reports of the successful use of Q $\beta$   
20 replicase to perform either linear or exponential amplification across the full spectrum of target  
21 nucleic acids.

22       **267.** This lack of enablement of Examples 6 and 7 is even more significant when the  
23 Court considers the "promised" disclosure of those Examples. While Examples 4 and 5 purport to  
24 disclose linear amplification only, Examples 6 and 7 represent the *only* disclosure of the *only*  
25 commercially viable amplification techniques encompassed by the patent.<sup>4</sup> Consequently,

26       <sup>4</sup> The linear amplification methods of Examples 4 and 5 are largely irrelevant. Only exponential  
27 amplification has significant utility. Vysis' own expert, Dr. David Persing has characterized  
28 exponential amplification as "the hallmark of a nucleic acid amplification method." Dr. Persing,  
"In Vitro Nucleic Acid Amplification Techniques," *Diagnostic Molecular Microbiology* at 51  
(1993). In any event, as set forth in Section II, above, no scientist at Gene Trak ever attempted the

1 although Gene Trak's failure to enable 50% of the disclosed preferred embodiments should be  
2 singularly sufficient to render the claims invalid, its failure to enable 100% of the commercially  
3 viable claims should be conclusive. Further, the same considerations that demonstrate lack of  
4 enablement of Examples 6 and 7 suggest lack of enablement of Examples 4 and 5.

5 268. The claims of the '338 patent are therefore invalid for lack of enablement.

6 **2. Obviousness, Anticipation and Prior Public Disclosure.**

7 269. Section 103 of the Patent Act provides that "[a] patent may not be obtained . . . if  
8 the differences between the subject matter sought to be patented and the prior art are such that the  
9 subject matter as a whole would have been obvious at the time the invention was made to a person  
10 having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103. Consistent  
11 with the language of the statute, the Federal Circuit has confirmed that trial courts must consider  
12 the invention as a whole and consider the claims in their entirety. *See, e.g., W.L. Gore & Assocs.*  
13 *v. Garlock, Inc.*, 721 F.2d 1540, 1551 (Fed. Cir. 1983); *Medtronic, Inc. v. Cardiac Pacemakers,*  
14 *Inc.*, 721 F.2d 1563, 1567 (Fed. Cir. 1983). The Federal Circuit has repeatedly confirmed that the  
15 issue of obviousness is based upon factual determinations. *See, e.g., Monarch Knitting Machinery*  
16 *Corp. v. Sulzer Morat GMBH*, 139 F.3d 877, 881 (Fed. Cir. 1998) ("Obviousness is ultimately a  
17 determination of law based on underlying determinations of fact."); *Richardson-Vicks, Inc. v.*  
18 *Upjohn Co.*, 122 F.3d 1476, 1479 (Fed. Cir. 1997). Those factual determinations include: (1) the  
19 scope and content of the prior art; (2) the differences between the prior art and the properly  
20 construed claims; (3) the level of ordinary skill in the art at the time of the invention; and (4)  
21 objective evidence of non-obviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 86 S.Ct.  
22 684, 693-94 (1966).

23 270. Where it is contended that multiple references, considered together, make the  
24 invention obvious, the relevant inquiry for determining the scope and content of the prior art is  
25 "whether there is a reason, suggestion, or motivation in the prior art or elsewhere that would have  
26 led one of ordinary skill in the art to combine the references." *Ruiz v. A.B. Chance Co.*, 234 F.3d

27  
28 experiments of Example 4 or 5.

1 654, 664 (Fed. Cir. 2000).

2 271. In appropriate circumstances, a single prior art reference can render a claim  
3 obvious. *Sibia Neurosciences, Inc. v. Cadus Pharmaceutical Corp.* 225 F.3d 1349, 1356 (Fed. Cir.  
4 2000); *B.F. Goodrich Co. v. Aircraft Braking Sys. Corp.*, 72 F.3d 1577, 1582 (Fed. Cir. 1996). A  
5 single prior art reference can render a claim obvious if there exists a suggestion or motivation to  
6 modify the teachings of that reference to the claimed invention in order to support the obviousness  
7 conclusion. *Sibia Neurosciences, supra*, 225 F.3d at 1356; *B.F. Goodrich, supra*, 72 F.3d at 1582.

8 272. The suggestion or motivation to combine references or to modify the teachings of a  
9 single reference may be derived from the prior art reference itself, from the knowledge of one of  
10 ordinary skill in the art, or from the nature of the problem to be solved. *Ruiz, supra*, 234 F.3d at  
11 665; *Sibia Neurosciences, supra*, 225 F.3d at 1356.

12 273. Determining whether there is a suggestion or motivation to combine references or  
13 modify a single prior art reference is one aspect of determining the scope and content of the prior  
14 art, a fact question subsidiary to the ultimate conclusion of obviousness. *Sibia Neurosciences,*  
15 *supra*, 225 F.3d at 1356.

16 274. A patent may also be invalid based on anticipation under Section 102 of the Patent  
17 Act. 35 U.S.C. § 102(a) provides that one cannot obtain a patent for an invention that “was known  
18 or used by others in this country, or patented or described in a printed publication in this or a  
19 foreign country, before the invention thereof by the applicant for patent.” Section 102(a) therefore  
20 establishes that a person cannot patent what was already known to others. “If the invention was  
21 known to or used by others in this country before the date of the patentee’s invention, the later  
22 inventor has not contributed to the store of knowledge, and has no entitlement to a patent.”  
23 *Woodland Trust v. Flowertree Nursery, Inc.*, 148 F.3d 1368, 1370 (Fed. Cir. 1998). Accordingly,  
24 in order to invalidate a patent based on prior knowledge or use, that knowledge or use must have  
25 been available to the public. *See, e.g., Carella v. Starlight Archery*, 804 F.2d 135, 139 (Fed. Cir.  
26 1986) (the § 102(a) language “known or used by others in this country” means knowledge or use  
27 which is accessible to the public); *Constant v. Advanced Micro-Devices, Inc.*, 848 F.2d 1560, 1568  
28 (Fed. Cir. 1988) (The term “printed publication” means that “before the critical date the reference

1 must have been sufficiently accessible to the public interested in the art . . . .”).

2 275. “[A] claim is anticipated if each and every limitation is found either expressly or  
3 inherently in a single prior art reference.” *Celeritas Techs., Ltd. v. Rockwell Int’l Corp.*, 150 F.3d  
4 1354, 1360 (Fed. Cir. 1998). Whether a claim limitation is inherent in a prior art reference is a  
5 factual issue on which evidence may be introduced. *In re Schreiber*, 128 F.3d 1473, 1477, 44  
6 USPQ2d 1429, 1431 (Fed.Cir.1997). Anticipation is a question of fact, which must be established  
7 by clear and convincing evidence. *See Hoover Group, Inc. v. Custom Metalcraft, Inc.*, 66 F.3d  
8 299, 302 (Fed. Cir. 1995); *Shearing v. Iolab Corp.*, 975 F.2d 1541, 1544 (Fed. Cir. 1992).

9 276. “Anticipation” and “obviousness” are determined as of the date of the invention,  
10 which is presumed to be the filing date of the patent application. *Ecolochem, Inc. v. Southern*  
11 *California Edison Co.*, 227 F.3d 1361, 1371 (Fed. Cir. 2000); *Gamma-Metrics, Inc. v. Scantech*  
12 *Ltd.*, 52 USPQ2d 1579, 1585 (S.D. Cal. 1998).

13 277. Under 35 U.S.C. § 102(b), a patent is invalid if the invention was described in a  
14 printed publication in any country more than one year prior to the date of the application for the  
15 patent in the United States.

16 a. **Vysis’ claim of priority for the ‘338 patent is invalid and the**  
17 **effective filing date of the ‘080 application is no earlier than**  
**January 31, 1991.**

18 278. The ‘338 patent issued from U.S. patent application no. 08/238,080 (the “ ‘080  
19 application”), filed May 3, 1994. However, Vysis contends that the ‘080 application is entitled to  
20 claim the benefit of at least five prior patent applications and thus to an effective filing date of  
21 December 21, 1987.

22 279. Gen-Probe disputes that the ‘080 application is entitled to *any* filing date earlier  
23 than the date of the ‘080 application itself, and alternatively contends that the ‘080 application is  
24 not entitled to any filing date earlier than January 31, 1991, the filing date of U.S. patent  
25 application 07/648,468.

26 280. 35 U.S.C. § 120 sets forth the requirements that must be met before an application  
27 is entitled to the benefit of an early filing date in the United States. The requirements include the  
28 following: First, the application must be “for an invention disclosed in the manner provided by the

1 first paragraph of section 112 . . . in an application previously filed in the United States;" second,  
2 the application which claims the benefit must be co-pending with the earlier application or with an  
3 application which is itself entitled to the benefit of the earlier date; and third, there must be a  
4 "specific reference" in the later filed application to the "earlier filed application."

5       **281.** Vysis has the burden of proving that the requirements of 35 U.S.C. § 120 have been  
6 satisfied by each prior patent application in the chain of applications that make up its claim of  
7 priority and that it is therefore entitled to claim the benefit of December 21, 1987 as the filing date.  
8 *Kubota v. Shibuya*, 999 F.2d 517, 521 (Fed.Cir. 1993); *Bloch v. Chiatse Sze*, 484 F.2d 1202  
9 (CCPA 1973).

10       **282.** As part of its claim of priority for the '338 patent, Vysis claims that U.S. patent  
11 application 07/136,920 is entitled to the benefit of earlier-filed application 06/922,155. However,  
12 the '920 application is not entitled to the benefit of the filing date of the '155 application under 35  
13 U.S.C. § 120 because the '155 application does not disclose the invention claimed in the '920  
14 application in the manner provided by the first paragraph of 35 U.S.C. § 112.

15       **283.** As part of its current claim of priority for the '338 patent, Vysis claims that U.S.  
16 patent application 07/648,468 is entitled to the benefit of earlier-filed application 07/644,967.  
17 However, the '468 application is not entitled to the benefit of the filing date of the '967  
18 application, for several reasons.

19       **284.** First, under 35 U.S.C. §§ 120 and 133, the post-abandonment amendment made by  
20 Vysis to the '468 application to claim priority from the '867 application is legally invalid, null, and  
21 void because Vysis did not revive the '468 application pursuant to 35 U.S.C. § 133 and 37 C.F.R. §  
22 1.137(a) or pursuant to 35 U.S.C. § 41(a)(7) and 37 C.F.R. § 1.137(b) and did not make the  
23 amendments in good faith and with honesty. An abandoned intermediate patent application may  
24 not be amended after patent issuance without the applicant seeking revival of such application and  
25 satisfying the requirements of the applicable revival regulations. Congress has required that such  
26 applications be deemed "abandoned" (35 U.S.C. § 133). Congress and the Commissioner have  
27 provided that abandoned applications may be "revived" only when certain particular requirements  
28 are met. (35 U.S.C. §§ 41(a)(7), 133; 37 C.F.R. § 1.137.) Vysis did not petition to revive the

1 applications prior to amending them and could not have satisfied the statutory and regulatory  
2 requirements for revival. Vysis simply made amendments to the abandoned applications, without  
3 reviving them. While the PTO entered the amendments, such entry was invalid under 35 U.S.C. §  
4 133. *Baxter International, Inc. v. McGraw, Inc.*, 19 F.3d 1321, 1334 (Fed. Cir. 1998); *Exxon Corp.*  
5 *v. Phillips Petroleum*, 1999 U.S. Dist. Lexis 20806 (S.D. Tex. 1999). Section 133 expressly  
6 provides that an application must be regarded as abandoned if the application fails to prosecute the  
7 application within 6 months of any action by the PTO. Section 133 sets forth a congressional  
8 mandate. Any application which is to be “regarded as abandoned” pursuant to 35 U.S.C. § 133  
9 must be treated by the PTO and the courts as abandoned. *Lindsay v. Stein*, 10 F. 907, 913  
10 (C.C.N.Y. 1882). The abandonment of an application results in the *final* termination of *all*  
11 proceedings on the application. *Manual of Patent Examining Procedures (“MPEP”)* § 201.11 at  
12 200-53 (Rev 1., Feb. 2000); *see also* MPEP § 203.05 at 200-77 (Rev 1., Feb. 2000) (Abandoned  
13 applications are immediately removed from the PTO docket of pending applications); *accord*, 4  
14 *Chisum on Patents* § 13.05 at 13-41 (2000). An abandoned application cannot be regarded as  
15 available for amendment:

16                   An application which is to be ‘regarded as abandoned’ must be  
17                   regarded as abandoned by the commissioner and the courts, and, if it  
18                   is regarded as abandoned, it cannot be regarded as subsisting ...

18 *Lindsay v. Stein*, 10 F. 907, 913 (C.C.N.Y. 1882). Or, to be put more bluntly, abandonment of a  
19 patent application turns it into a “dead body.” *Struthers Patent Corp. v. Nestle Co.*, 558 F. Supp.  
20 747, 811 (D.N.J. 1981), *aff’d*, 709 F.2d 1493 (3d Cir. 1982), *cert. denied*, 464 U.S. 915 (1983).  
21 Congress has provided two statutes that permit an applicant to revive an abandoned application.  
22 First, 35 U.S.C. § 133 provides that, if an applicant fails to prosecute an application within a  
23 specified time, then the application shall become abandoned, “unless it be shown to the satisfaction  
24 of the Commissioner<sup>5</sup> of the Patent and Trademark Office that such delay was unavoidable.” 35  
25 U.S.C. § 133. Pursuant to this statute, the Commissioner has enacted a comprehensive set of

26  
27                   <sup>5</sup> Effective March 29, 2000, the Commissioner of the PTO became known as the  
28                   “Director” of that office. However, because the statutes and cases cited in this memorandum  
                    uniformly use the former title, the term “Commissioner” will be used here for clarity’s sake.



1 regulations governing the procedures and substantive requirements for revival. 37 C.F.R. § 1.137  
2 (a). Second, a more recently enacted statute, 35 U.S.C. § 41(a)(7), provides that an applicant may  
3 file a petition for revival of an “unintentionally abandoned” application. The Commissioner has  
4 also adopted a comprehensive set of regulations governing the procedures and substantive  
5 requirements for revival under this statute. 37 C.F.R. § 1.137 (b). An abandoned intermediate  
6 patent application may not be amended after patent issuance without the applicant seeking revival  
7 of such application and satisfying the requirements of the applicable revival regulations. 35 U.S.C.  
8 § 133. *See also Air Products and Chemicals v. Quigg*, 8 USPQ2d 2015 (D.D.C. 1988); *Sampson*  
9 *v. Ampex Corp.*, 335 F.Supp. 242 (S.D.N.Y. 1971), *aff’d*, 463 F.2d 1042 (2d Cir. 1972); *In re*  
10 *Application G*, 11 USPQ2d 1378 (Commr. Pat 1989). Otherwise, such an application must be  
11 regarded as truly abandoned, a “dead body,” and not available for amendment. The PTO’s own  
12 rules recognize that:

13           When an amendment is filed after the expiration of the statutory  
14           period [for response to a PTO rejection], the application is  
            abandoned *and the remedy is to petition to revive it*.

15 MPEP § 711.02 at 700-84 (Rev 1., Feb. 2000). The Board of Patent Appeals and courts have  
16 refused to recognize amendments made to abandoned patent applications. *See, e.g., Lorenz v.*  
17 *Finkl*, 333 F.2d 885, 895-896 (C.C.P.A. 1964); *Struthers Patent Corp. v. Nestle Co.*, 558 F.Supp.  
18 747, 811 (D.N.J. 1981), *aff’d*, 709 F.2d 1493 (3d Cir. 1982), *cert. denied*, 464 U.S. 915 (1983).  
19 As applied to this case, the regulations and cases show that the intermediate patent application was  
20 required by 35 U.S.C. § 133 to be regarded as abandoned and thus “dead” for all purposes unless  
21 revived according to the statute and regulations. Given that defendant Vysis never attempted to  
22 revive these applications, Vysis could not amend these applications to change the priority claim.  
23 Furthermore, if an abandoned application may be amended without revival, amendment may be  
24 permitted only if the applicant has conducted itself at all times with good faith and honesty, a  
25 standard that Vysis cannot meet. Because Vysis’ amendments to these applications are null and  
26 void, the applications do not contain the required “specific reference” to earlier-filed applications  
27 that is essential for such applications to provide priority under section 120.

28           **285.** Second, U.S. patent application 07/648,468 is not entitled to the benefit of the filing

1 date of the '967 application because the claims of the '468 application are not disclosed in the '967  
2 application in the manner provided by the first paragraph of 35 U.S.C. § 112, as required by 35  
3 U.S.C. § 120. Section 120 gives the benefit of a prior application's filing date only to the  
4 "invention" that is the subject to the later application, *if* that particular invention was adequately  
5 disclosed in the prior application. At least one claim of the subsequent application must be  
6 disclosed in the prior application in order for the subsequent application to have the benefit of the  
7 filing date of the earlier application under section 120. *Martin v. Johnson*, 454 F.2d 746, 750  
8 (CCPA 1972); *In re Scheiber*, 199 USPQ 782, 784 (CCPA 1978); *In re Lukach*, 442 F.2d 967,  
9 968, 169 USPQ 795, 796 (1971); *In re Brower*, 433 F.2d 813, 817, 167 USPQ 684, 687 (1970); *In*  
10 *re Kirchner*, 305 F.2d 897, 900, 904 (CCPA 1962); Chisum on Patents § 13.02 [4] at 13-11  
11 (1999). No claim of the '468 application is disclosed in the '967 application in the manner  
12 provided by the first paragraph of 35 U.S.C. § 112. In order for a patent application to be entitled  
13 to the benefit of the filing date of an earlier application, the prior application must disclose the  
14 invention claimed in the subsequent application sufficiently to provide an adequate written  
15 description of the invention:

16           An application for a patent for an invention **disclosed in the manner**  
17           **provided in the first sentence of section 112 of this title in an**  
18           **application previously filed in the United States** by the same  
          inventor ... shall have the same effect, **as to such invention**, as  
          though filed on the date of the prior application....

19 35 U.S.C. § 120. The chain of patent applications relied on by Vysis for its claim of priority for  
20 the '338 patent fail to satisfy this requirement of section 120. The PTO repeatedly recognized that  
21 the invention of the '468 application was not disclosed in the prior '920 application.

22           **286.** Third, U.S. patent application 07/648,468 is not entitled to the benefit of the filing  
23 date of the '967 application with respect to later-filed method claims in light of the fact that the  
24 '468 application was filed in response to a restriction requirement by the U.S. Patent and  
25 Trademark Office and the applicant was thereafter required to act consistently (i.e., maintain  
26 consonance) with such election. *Gerber Garment Technology Inc. v. Lectra Systems Inc.*, 16  
27 USPQ2d 1437, 1440-1441 (Fed. Cir. 1990); *Pennwalt Corp. v. Akzona Inc.*, 222 USPQ 833 (Fed.  
28 Cir. 1984).

1           **287.** As part of a previous claim of priority for the '338 patent, Vysis contended that  
2 U.S. patent application 07/648,468 was directly entitled to the benefit of earlier-filed application  
3 07/136,920. Vysis no longer makes such a contention of direct benefit. If such a contention is re-  
4 instituted, the '468 application is not directly entitled to the benefit of the filing date of the '920  
5 application, for several reasons.

6           **288.** First, the '920 application was not pending at the time the '468 application was  
7 filed.

8           **289.** Second, the '468 application would not be entitled under 35 U.S.C. § 120 to the  
9 earlier filing date of the '920 application in light of the fact that no claim of the '468 application is  
10 disclosed in the '920 application in the manner provided by the first paragraph of 35 U.S.C. § 112.  
11 At least one claim of the subsequent application must be disclosed in the prior application in order  
12 for the subsequent application to have the benefit of the filing date of the earlier application under  
13 section 120. *Martin, supra*, 454 F.2d at 750; *In re Scheiber, supra*, 199 USPQ at 784; *In re*  
14 *Lukach, supra*, 442 F.2d at 968, 169 USPQ at 796; *In re Brower, supra*, 433 F.2d at 817, 167  
15 USPQ at 687; *In re Kirchner, supra*, 305 F.2d at 904; Chisum on Patents § 13.02 [4] at 13-11  
16 (1999).

17           **290.** Third, the '468 application would not be entitled to the benefit of the filing date of  
18 the '920 application with respect to later-filed method claims in light of the fact that the '468  
19 application was filed in response to a restriction requirement by the U.S. Patent and Trademark  
20 Office and the applicant was thereafter required to act consistently (i.e., maintain consonance) with  
21 such election. *Gerber Garment Technology Inc. v. Lectra Systems Inc.*, 16 USPQ2d 1437, 1440-  
22 1441 (Fed. Cir. 1990); *Pennwalt Corp. v. Akzona Inc.*, 222 USPQ 833 (Fed. Cir. 1984).

23           **291.** As part of its current claim of priority for the '338 patent, Vysis claims that U.S.  
24 patent application 07/946,749 is indirectly entitled to the benefit of the earlier-filed application  
25 '967 application. However, the '749 application is not entitled to the benefit of the filing date of  
26 the '967 application, for several reasons.

27           **292.** First, under 35 U.S.C. §§ 120 and 133, the post-abandonment amendment made by  
28 Vysis to the '749 application to include a specific reference to the '967 application is legally

1 invalid, null, and void for the reasons set forth hereinabove.

2       **293.** Second, the '749 application is not entitled to the benefit of the filing date of the  
3 '967 application because no claim in the '468 and '749 applications was disclosed in the '967  
4 application in the manner provided by the first paragraph of 35 U.S.C. § 112, as set forth  
5 hereinabove.

6       **294.** Third, the '749 application is not entitled to the benefit of the filing date of the '967  
7 application with respect to later-filed method claims in light of the fact that the '468 and '749  
8 applications were filed in response to a restriction requirement by the Patent Office and the  
9 applicant was thereafter required to act consistently (i.e., maintain consonance) with such election,  
10 as set forth hereinabove.

11       **295.** As part of its current claim of priority for the '338 patent, Vysis claims that U.S.  
12 patent application 08/124,826 is indirectly entitled to the benefit of the earlier-filed application  
13 '967 application. However, the '826 application is not entitled to the benefit of the filing date of  
14 the '967 application, for several reasons.

15       **296.** First, under 35 U.S.C. §§ 120 and 133, the post-abandonment amendment made by  
16 Vysis to the '826 application to include a specific reference to the '967 application is legally  
17 invalid, null, and void for the reasons set forth hereinabove.

18       **297.** Second, the '826 application is not entitled to the benefit of the filing date of the  
19 '967 application because no claim in the '468, '749, and '826 applications was disclosed in the  
20 '967 application in the manner provided by the first paragraph of 35 U.S.C. § 112, as set forth  
21 hereinabove.

22       **298.** Third, the '826 application is not entitled to the benefit of the filing date of the '967  
23 application with respect to later-filed method claims in light of the fact that the '468, '749 and '826  
24 applications were filed in response to a restriction requirement by the Patent Office and the  
25 applicant was thereafter required to act consistently (i.e., maintain consonance) with such election,  
26 as set forth hereinabove.

27       **299.** As part of its current claim of priority for the '338 patent, Vysis claims that U.S.  
28 patent application 08/238,080 is entitled to the benefit of the earlier-filed application '826

1 application. However, the '080 application is not entitled to the benefit of the filing date of the  
2 '826 application, for several reasons.

3       300. First, the certificate of correction obtained by Vysis after the issuance of the '338  
4 patent, changing the claim of priority from U.S. patent application 08/400,657 to U.S. patent  
5 application 08/124,826 is invalid and ineffective because that certificate of correction could not  
6 and did not amend the '080 application itself. The certificate therefore did not change the effective  
7 date of the '080 application under the literal language of 35 U.S.C. § 120, which requires that the  
8 application for the patent be amended. *See Sampson v. Ampex Corp.*, 333 F.Supp. 59, 63  
9 (S.D.N.Y. 1971).

10       301. Second, the certificate of correction obtained by Vysis after the issuance of the '338  
11 patent, changing the claim of priority from U.S. patent application 08/400,657 to U.S. patent  
12 application 08/124,826 is invalid because Vysis' request for the certificate of correction did not  
13 meet the statutory requirements for a certificate of correction under 35 U.S.C. § 255. Section 255  
14 permits a patentee to seek a certificate of correction "whenever a mistake of a clerical or  
15 typographical nature, or of minor character, which was not the fault of the Patent and Trademark  
16 Office, appears in a patent and a showing has been made that such mistake occurred in good faith."  
17 In *Superior Fireplace Co. v. Majestic Products Co.*, 270 F.3d 1358, 1375 (Fed. Cir. 2001), the  
18 Federal Circuit interpreted the statutory requirement that a mistake subject to "correction" be one  
19 "of minor character." In affirming the district court's summary judgment that the certificate of  
20 correction obtained by the patentee was invalid, the Federal Circuit held that a mistake that, if  
21 corrected, would avoid certain invalidity of the patent "must be viewed as highly important and  
22 thus *cannot be a mistake of minor character.*" *Superior Fireplace, supra*, 270 F.3d at 1375  
23 (emphasis added). Under this precedent, as a matter of law, a substantive change to a patentee's  
24 claim of priority that saves a patent from invalidity cannot qualify as a "a mistake of minor  
25 character." *Superior Fireplace, supra*, 270 F.3d at 1375 ; *see also In re Arnott*, 19 USPQ2d 1049  
26 (Comm'r Pat. Trademarks 1991). The '080 application's claim of priority to the '826 application  
27 was not "a mistake of a clerical or typographical nature, or of minor character." *Superior*  
28 *Fireplace, supra*, 270 F.3d at 1376; *In re Arnott, supra*, 19 USPQ2d at 1049; *See also Brenner v.*

1 *State of Israel*, 400 F.2d 789, 158 USPQ 584 (D.C. Cir. 1968). Additionally, the mistake was not  
2 inadvertent. Vysis made deliberate, reasoned choices with respect to its claim of priority to the  
3 '657 application. A deliberate choice does not result in a "mistake" within the scope of 35 U.S.C. §  
4 255. See *In re Orita*, 550 F.2d 1277, 193 USPQ 145 (C.C.P.A. 1977) (applicant could not  
5 establish "inadvertence, accident, or mistake" for purposes of reissue where defect resulted from  
6 deliberate choice); *In re Mead*, 198 USPQ 412 (C.C.P.A. 1978) (same). Furthermore, if the '080  
7 application's claim of priority to the '826 application was "a mistake of a clerical or typographical  
8 nature, or of minor character," such mistake did not occur in good faith. The applicant's overall  
9 course of conduct with respect to the prosecution of applications for the '338 patent, particularly  
10 after the abandonment of the '505 application, demonstrates the applicant's lack of good faith. If  
11 the certificate of correction is valid and effective, it does not apply to Gen-Probe. Gen-Probe  
12 acquired intervening rights prior to issuance of certificate of correction. A certificate of correction  
13 does not affect causes of action that accrued before it was issued. *Southwest Software Inc. v.*  
14 *Harlequin Inc.*, 56 USPQ2d 1161 (Fed. Cir. 2000).

15       **302.** Third, no claim of the '080 application is disclosed in the '826 application in the  
16 manner provided by the first paragraph of 35 U.S.C. § 112, as required by 35 U.S.C. § 120. At  
17 least one claim of the subsequent application must be disclosed in the prior application in order for  
18 the subsequent application to have the benefit of the filing date of the earlier application under  
19 section 120. *Martin, supra*, 454 F.2d at 750; *In re Scheiber, supra*, 199 USPQ at 784; *In re*  
20 *Lukach, supra*, 442 F.2d at 968, 169 USPQ at 796; *In re Brower, supra*, 433 F.2d at 817, 167  
21 USPQ at 687; *In re Kirchner, supra*, 305 F.2d at 900, 904; Chisum on Patents § 13.02 [4] at 13-11  
22 (1999). Adequate "disclosure" under sections 120 and 112 with respect to an invention claimed in  
23 a prior application may not be accomplished solely by a conclusory boilerplate "incorporation by  
24 reference." *Maine Manufacturing Co. v. U.S. International Trade Commission*, 37 USPQ2d 1609,  
25 1614 (Fed. Cir. 1996); *Ex Parte Raible*, 8 USPQ2d 1709, 1710 (Bd. Pat. App. 1988); *Ex Parte*  
26 *McGrath*, 109 USPQ 70, 72 (Bd. Pat. App. 1955). Conclusory boilerplate "incorporation by  
27 reference" is particularly ineffective for purposes of section 120 when the earlier application was  
28 filed in response to a restriction requirement by the PTO, for such incorporation violates principles

1 of consonance, see *Gerber Garment Technology Inc. v. Lectra Systems Inc.*, 16 USPQ2d 1437,  
2 1440-1441 (Fed. Cir. 1990); *Pennwalt Corp. v. Akzona Inc.*, 222 USPQ 833 (Fed. Cir. 1984), and  
3 where the inventors on the two applications are not the same.

4 303. Fourth, the '080 application is not entitled to the benefit of the filing date of the  
5 '826 application in light of the fact that the '468 application and all subsequent device applications  
6 were filed in response to a restriction requirement by the Patent Office and the applicant was  
7 thereafter required to act consistently (i.e., maintain consonance) with such election. *Gerber*  
8 *Garment Technology Inc. supra*, 16 USPQ2d at 1440-1441; *Pennwalt Corp., supra*, 222 USPQ at  
9 833.

10 304. As part of a previous claim of priority for the '338 patent, Vysis contended that the  
11 '080 application was entitled to the benefit of application 08/400,657. Vysis no longer makes such  
12 a contention. If such a contention is re-instituted, the '080 application is not entitled to the benefit  
13 of the filing date of the '657 application, for several reasons.

14 305. First, the '657 application was not pending at the time the '080 application was  
15 filed. 35 U.S.C. § 120.

16 306. Second no claim of the '080 application is disclosed in the '657 application in the  
17 manner provided by the first paragraph of 35 U.S.C. § 112 as required by 35 U.S.C. § 120, as  
18 discussed hereinabove.

19 307. To the extent that Vysis claims that the '468 application was filed at least in part as  
20 a divisional application to the '920 application in response to the Patent Office's restriction  
21 requirement in the '920 application, the '080 application is still not entitled to the benefit of the  
22 filing date of the '657 application in light of the fact that the such a claim to priority would be  
23 inconsistent with that prior election, as discussed hereinabove.

24 **b. The '338 patent is invalid under 35 U.S.C. § 102(b) in light of the**  
25 **public disclosure of the invention on August 23, 1989.**

26 308. Because the priority date of the '338 patent is no earlier than January 31, 1991, the  
27 patent is invalid pursuant to 35 U.S.C. § 102(b) in light of the public disclosure on August 23, 1989  
28 of the invention claimed in the '338 patent, upon publication of Vysis' application for European

1 Patent publication no. 0 328 829 A2. *Baxter International, Inc. v. McGaw, Inc.*, 149 F.3d 1321  
2 (Fed. Cir. 1998).

3 309. Furthermore, even ignoring the procedural defects that should limit the priority date  
4 to January 31, 1991, to the extent that the Court determines that Vysis' priority date is limited to  
5 May 24, 1994 (the filing date of the '080 application), the above-referenced publication of the PCT  
6 application corresponding to the '338 patent would similarly render the '338 patent invalid under  
7 35 U.S.C. 102(b).

8 c. **The invention claimed in the '338 patent is obvious and**  
9 **anticipated even if the effective filing date of the '080 application**  
10 **is December 21, 1987.**

11 310. The invention claimed in the '338 Patent would have been obvious to one of  
12 ordinary skill in the art as of December 21, 1987, if the '338 patent is entitled to such filing date.  
13 Specifically, and as set forth in Section II, above, before December 21, 1987, it was common  
14 practice to isolate a target polynucleotide from a sample by contacting the sample with a solid  
15 support that bound to the target polynucleotide either directly or indirectly. The support with its  
16 attached polynucleotide and bound target polynucleotide was separated from the sample,  
17 effectively separating the target from other sample components that could interfere with further  
18 manipulation of the target polynucleotide. It was also well known in the art that amplifying the  
19 target polynucleotide directly or by producing an amplified signal based upon the presence of the  
20 target polynucleotide could increase detection sensitivity. It would have been obvious to one of  
21 ordinary skill in the art in December 1987 to perform the combination of those manipulations for  
22 the purpose of detecting the presence of a target polynucleotide in a sample. One of ordinary skill  
23 would have been motivated to combine both target polynucleotide capture and amplification to  
24 ensure success in a detection assay.

25 311. The examples of the '338 patent that disclose amplification disclose only non-  
26 specific amplification of the target polynucleotide. Particularly where the amplification method to  
27 be used is non-specific, it would have been obvious to one of ordinary skill in the art to use a  
28 specific capture step prior to amplification. Prior to December 21, 1987, it was well known to  
those skilled in the art that specificity had to be provided in some step of every biologic assay.



1 Prior to December 21, 1987 it was known that nucleic acid sequences could be attached to solid  
2 supports such as magnetic beads in order to specifically capture a complementary nucleic acid of  
3 interest. Thus as of December 27, 1987, it would have been obvious to one skilled in the art to use  
4 a specific capture step to isolate the target nucleic acid prior to non-specific amplification. Unless  
5 the target was isolated, non-specific amplification would not solve the problem that amplification  
6 was originally intended to address. Non-specific amplification of an entire sample, without a  
7 separation step, would not be likely to increase the amount of signal over background generated by  
8 the hybridization of detector probe to target. This was known by those of ordinary skill in the art  
9 and was also disclosed in the prior art as of December 21, 1987.

10 312. In addition to being obvious, the claimed invention of the '338 patent is anticipated  
11 by each of Arsenyan et al., Gaubatz et al., Powell et al., Chu, et al and Feix et al. 1987.

12 313. There are no relevant secondary considerations of non-obviousness in this case  
13 other than Vysis' own lack of commercial success. Secondary considerations are relevant, if at all,  
14 only when they directly relate to the invention(s) expressly claimed in the patent at issue. *See,*  
15 *Sjolund v. Musland*, 847 F.2d 1573, 1582 (Fed. Cir. 1988); *In re Vamco Machine & Tool, Inc.*, 752  
16 F.2d 1564, 1577 (Fed. Cir. 1985). Gen-Probe's products, and its conduct with respect to TMA  
17 technology, are irrelevant because they do not involve the claimed invention. Further, Gen-  
18 Probe's conduct and products are remote in time to the alleged date of invention. Vysis cannot  
19 show the required nexus between the license obtained by Gen-Probe and the merits of invention  
20 claimed in the '338 patent. *In re GPAC, Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995).

21 C. THE '338 PATENT IS UNENFORCEABLE ON THE GROUND OF PROSECUTION  
22 LACHES.

23 314. Applicants intentionally, unreasonably, and inexcusably delayed in the prosecution  
24 of the invention claimed in the '338 patent. Gen-Probe was injured by such delay.

25 315. The equitable doctrine of laches bars enforcement of patent claims that were issued  
26 following unreasonable and unexplained delay, where such delay causes injury to an alleged  
27 infringer and others.

28 316. The intent of the patent statute has always been to grant patent rights for a limited

1 time. The law has not approved of delays before filing and during prosecution which extend the  
2 period of patent rights or otherwise injure others. Any practice by inventors through which they  
3 deliberately and without excuse postpone the beginning of the patent monopoly is an evasion of  
4 the patent statute and defeats its benevolent aim. *In re Bogese*, 22 USPQ2d 1821 (Comr Pat. 1991).

5 **D. THE '338 PATENT IS UNENFORCEABLE DUE TO INEQUITABLE CONDUCT BY**  
6 **APPLICANTS.**

7 **317.** Applicants for patents have a duty to prosecute patent applications in the Patent  
8 Office with candor, good faith, and honesty. *Li Second Family Limited Partnership v. Toshiba*  
9 *Corp.*, 231 F.3d 1373, 1378 (Fed. Cir. 2000); 37 C.F.R. § 1.56.

10 **318.** A breach of this duty, which breach can include affirmative misrepresentations of  
11 material facts, failure to disclose material information, or submission of false material information,  
12 coupled with an intent to deceive, constitutes inequitable conduct. *Li Second Family Limited*  
13 *Partnership, supra*, 231 F.3d at 1378. Inequitable conduct renders a patent unenforceable. *Id.*

14 **319.** Inequitable conduct requires a showing by clear and convincing evidence that the  
15 alleged nondisclosure or misrepresentation occurred, that the nondisclosure or misrepresentation  
16 was material, and that the patent applicant acted with the intent to deceive the PTO. *Id.* Once the  
17 threshold levels of materiality and intent have been established, the trial court must weigh  
18 materiality and intent to determine whether the equities warrant a conclusion that inequitable  
19 conduct occurred. *Id.*

20 **320.** The more material the information misrepresented or withheld by the applicant, the  
21 less evidence of intent will be required in order to find that inequitable conduct has occurred. *Id.*

22 **321.** Information is deemed material if there is a substantial likelihood that a reasonable  
23 examiner would have considered the information important in deciding whether to allow the  
24 application to issue as a patent, not whether the information would conclusively decide the issue of  
25 patentability. *Id.* at 1379-1380. Information concealed from the PTO may be material even  
26 though it would not invalidate the patent.

27 **322.** Materiality is not limited to "prior art," but instead embraces any information that a  
28 reasonable examiner would be substantially likely to consider important in deciding whether to

1 allow an application to issue as a patent. *GFI, Inc. v. Franklin Corp.*, 265 F.3d 1268, 1274 (Fed.  
2 Cir. 2001); *Akron Polymer Container Corp. v. Exxel Container, Inc.*, 148 F.3d 1380, 1382 (Fed.  
3 Cir. 1998).

4       **323.** Because the effective filing date of each claim in a patent application determines  
5 which references are available as prior art for purposes of §§ 102 and 103, information regarding  
6 the effective filing date is of the utmost importance to an examiner. Consequently, an applicant's  
7 misrepresentation that he is entitled to the benefit of an earlier filing date is highly material. *Id.* at  
8 1380.

9       **324.** Intent to deceive the PTO need not be proven by direct evidence. Indeed, direct  
10 proof of wrongful intent is rarely available but may be inferred from clear and convincing  
11 evidence of the surrounding circumstances. *Id.* The intent element of the offense is therefore in  
12 the main proven by inferences drawn from facts, with the collection of inferences permitting a  
13 confident judgment that deceit has occurred. *GFI, Inc., supra*, 265 F.3d at 1274.

14       **325.** When it is undisputed that a patent applicant was aware of a key reference and had  
15 otherwise been exposed to the work of the author of that reference, a strong case for deceptive  
16 intent is presented. *See, e.g., Id.* at 1274.

17       **1. The applicants engaged in inequitable conduct with respect to their**  
18       **claim of priority for the '338 patent.**

19       **326.** The applicants breached their duty of candor, good faith, and honesty to the Patent  
20 Office with respect to their claim of priority for the '338 patent by, among other things:

- 21       • Asserting a claim of priority for the '338 patent that claimed the benefit of a  
22       filing date of December 21, 1987.
- 23       • Failing to disclose and call attention to the abandonment of the '505 application  
24       in the course of prosecuting the '080 application.
- 25       • Failing to disclose and call to the Patent Office's attention, when claiming the  
26       '080 application as a divisional application from the '657 application, that the  
27       Patent Office had not imposed a restriction requirement as to the '657  
28       application, that the '657 application did not disclose the invention of the '080  
      application, and that the '657 application was not pending at the time the '080  
      application was filed.
- Failing to maintain consonance with the segregation of the method and device  
      inventions after the filing of applications 944,505 and 648,468, by amending  
      application no. 238,080 to allege that it was a divisional of application no.

400,657.

- Failing to maintain consonance with the segregation of the method and device inventions after the filing of applications 944,505 and 648,468, by changing the priority claim of the '338 patent to assert that the '080 application was a continuation of application no. 124,826.
- Engaging in the conduct described above with respect to the post-abandonment amendments to the '468, '749, and '826 applications.
- Engaging in the conduct described above with respect to the certificate of correction for the '338 patent.

327. The breaches alleged concerned material information and applicants' conduct was undertaken with the intent to deceive.

**2. The applicants engaged in inequitable conduct by failing to disclose material references and misrepresenting the state of the art.**

328. As noted in Section II, above, other facts evidencing inequitable conduct exist which render the '338 patent unenforceable. For example, during prosecution of the '080 application, material information known to the applicants that should have been disclosed to the Patent Office was not, in breach of the duty of candor. (See Paragraphs 183 through 204.) Further, applicants intentionally misrepresented the state of the art to the Patent Office (as discussed above).

329. Applicants' breaches of their duty of candor concerned material information and applicants' conduct was undertaken with the intent to deceive.

**3. The applicants engaged in other inequitable conduct.**

330. The non-enabling disclosures of the '338 patent also provide evidence of the applicants' inequitable conduct. For example, as discussed above, Example 7 is not enabling in that as of December, 1987, the superficial disclosures of Example 7 of the '338 patent did not enable one of ordinary skill in the art to use Q $\beta$  replicase to exponentially amplify heterologous RNAs. Example 7 constitutes a false example and a person of ordinary skill in the art, including the inventors of the '338 patent, would have known it was false.

331. Moreover, a reasonable examiner has no way of ascertaining whether or not a prophetic example, such as Example 7 is true or false. Accordingly, the examiner must assume it

1 is true. See Manual of Patent Examining Procedure (MPEP) §2164.04. In other words, when  
2 Example 7, which is a complete example, states, "Because the replication product is a template for  
3 the enzyme, the RNA is replicated exponentially.", the examiner is required by Patent Office  
4 policy to accept the statement as true unless the examiner has solid evidence to the contrary.  
5 When, as here, a patent applicant files a statement of operability in a patent application when the  
6 applicant is aware, at the time the application is filed that, he or she and those of ordinary skill in  
7 the art are not capable of operating the invention without undue experimentation, that patent  
8 applicant violates the duty of candor.

9       **332.** Further evidence of inequitable conduct exists with regard to Example 6 of the '338  
10 patent. As discussed above, Example 6 does not contain sufficient information to permit one of  
11 ordinary skill to carry out the amplification process without undue experimentation. Vysis'  
12 predecessor understood this to be the fact in that their documents show that Gene-Trak scientists  
13 tried but failed to achieve exponential amplification using the random primer amplification method  
14 described in Example 6. As a result, the efforts to practice the method set forth in Example 6 were  
15 abandoned.

16       **333.** Given these circumstances, one of ordinary skill in the art would not have known  
17 how to carry out the procedure set forth in Example 6. More importantly, since the applicants  
18 were aware of this inoperativeness of Example 6, the inclusion of the example constitutes an  
19 affirmative misrepresentation to the Patent Office regarding the scope of the claims.

20       **334.** Example 5 also provides evidence of inequitable conduct. The buffer purportedly  
21 used in Example 5 specifies concentrations of dNTP reagents that are too high to achieve  
22 amplification. Example 5 is therefore inoperative. Its inclusion in the patent constitutes an  
23 affirmative misrepresentation to the Patent Office regarding the scope of the claims

24       **E. VYSIS ABANDONED THE INVENTIONS CLAIMED IN THE '338 PATENT.**

25       **335.** As set forth above, on February 5, 1993, the applicants intentionally abandoned  
26 U.S. patent application 07/944,505 with full knowledge of their rights. Applicants thereafter,  
27 intentionally and with full knowledge of their rights, took no further action with respect to  
28 prosecuting claims for the inventions that had been the subject of the '505 application until May 3,

1 1994. Applicants elected this course of action (and inaction) in response to rejections by the  
2 Patent Office of the '920, '967, and '505 applications, of which certain of the office actions were  
3 first action final rejections.

4 336. Applicants' abandonment of the '505 application and subsequent inaction establish  
5 that applicants abandoned the inventions claimed therein in the United States. Applicants were  
6 thereafter precluded from obtaining a patent for any such inventions. Section 102 of Title 35,  
7 United States Code, provides as follows: "A person shall be entitled to a patent unless - ....(c) he  
8 has abandoned the invention ..."

9 337. Abandonment of the invention may be inferred from conduct that is inconsistent  
10 with active prosecution of claims. *United States Rifle & Cartridge Co. v. Whitney Arms Co.*, 118  
11 U.S. 22, 24 (1886); *MacBeth-Evans Glass Co. v. General Electric Co.*, 246 F. 695, 702 (6th Cir.  
12 1917). Therefore, intentional abandonment of a patent application is evidence supporting a  
13 contention of abandonment of the invention. *Lorenz v. Finkl*, 333 F.2d 885, 896, 142 USPQ 26  
14 (C.C.P.A. 1964) (Smith, J., concurring); *USM Corp. v. SPS Technologies, Inc.*, 514 F.Supp. 213,  
15 238 (N.D. Ill. 1981).

16 **F. VYSIS HAS COMMITTED ACTS OF UNFAIR COMPETITION.**

17 338. California Business & Professions Code § 17200 provides that "unfair competition  
18 shall mean and include any unlawful, unfair or fraudulent business act or practice . . . ." The  
19 California Supreme Court has defined "unfair" in the context of § 17200 to mean "conduct that  
20 threatens an incipient violation of an antitrust law, or violates the policy or spirit of one of those  
21 laws because its effects are comparable to or the same as a violation of the law, or otherwise  
22 significantly threatens or harms competition." *Cel-Tech Communications, Inc. v. Los Angeles  
23 Cellular Telephone Co.*, 20 Cal.4th 163, 186-87 (1999). Fraud in procuring a patent can give rise  
24 to antitrust liability in certain circumstances. *C.R. Bard, Inc. v. M3 Systems, Inc.*, 157 F.3d 1340,  
25 1367 (Fed. Cir. 1998) (citing *Walker Process Equip., Inc. v. Food Mach. & Chem. Corp.*, 382 U.S.  
26 172 (1965)). Conduct prohibited under antitrust law also "includes bringing suit to enforce a  
27 patent with knowledge that the patent is invalid or not infringed, and the litigation is conducted for  
28 anti-competitive purposes." *C.R. Bard*, 157 F.3d at 1358. Thus, a violation of the "policy or

spirit" of those antitrust laws would give rise to a § 17200 claim.

339. Coverage of unfair competition law has been characterized as "sweeping." *Id.* at 180. In fact, the "unfairness" prong of unfair competition law "is intentionally broad, thus allowing courts maximum discretion to prohibit new schemes to defraud." *Schnall v. Hertz Corp.*, 78 Cal.App.4th 1144 (2000); *see also Dow Chemical Co. v. Exxon Corp.*, 139 F.3d 1470, 1476 (Fed. Cir. 1998) (noting viability of unfair competition claim predicated in part on inequitable conduct).

340. Based on the facts set forth in Section II, above, the facts are clear that the claims of the '338 patent are invalid and unenforceable. Vysis was made aware of these facts when the underlying facts were made known to Vysis by Gen-Probe during discussions concerning settlement of prior, unrelated litigation between the parties. Vysis' enforcement of the '338 patent when it knew or reasonably should have known that the claims of the '338 patent were invalid and unenforceable constitutes unfair competition.

#### IV. EVIDENTIARY ISSUES

341. Gen-Probe does not presently anticipate any unusual evidentiary issues with the exception that there is a stipulated protective order governing the confidentiality of many of the documents produced by the parties in this action and which relate to highly confidential information concerning the parties' technology, ongoing research programs and collaborations with third parties. Due to the nature of the highly competitive environment in which the parties' operate, the protective order contemplates and directs the method of introduction and use by the parties of confidential information at trial.

342. Gen-Probe anticipates that it may be appropriate to file *in limine* motions concerning the evidence to be offered at trial, but Gen-Probe has not yet identified a complete list of specific issues to be addressed by such motions.

#### V. BIFURCATION OF ISSUES

343. Due to the importance of and substantial dispute regarding Vysis' claim of priority under 35 U.S.C. § 120 for the '338 patent, Gen-Probe contends that the issues associated with and the determination of the priority should be submitted for trial before the trial of other issues.

344. Gen-Probe contends that the merits of Gen-Probe's unfair competition claim should be reserved and submitted to trial after the trial and determination of other issues.

**VI. ABANDONED ISSUES**

345. There are no issues that have been abandoned by stipulation of the parties with the exception of a stipulation between the parties to the effect that Gen-Probe anticipates that its NAT test kits that use a combination of target capture and amplification will enjoy commercial success.

**VII. JURY TRIAL**

346. Both parties have timely requested a jury trial of all issues so triable.

**VIII. WITNESSES**

347. The list of witnesses that Gen-Probe presently anticipates offering at trial is set forth on Exhibit "A" hereto.

**IX. EXHIBITS**

348. The list of exhibits that Gen-Probe presently anticipates offering at the trial of this matter other than those to be used for impeachment are set forth in Exhibit "B" hereto.

Dated: January 14, 2002

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